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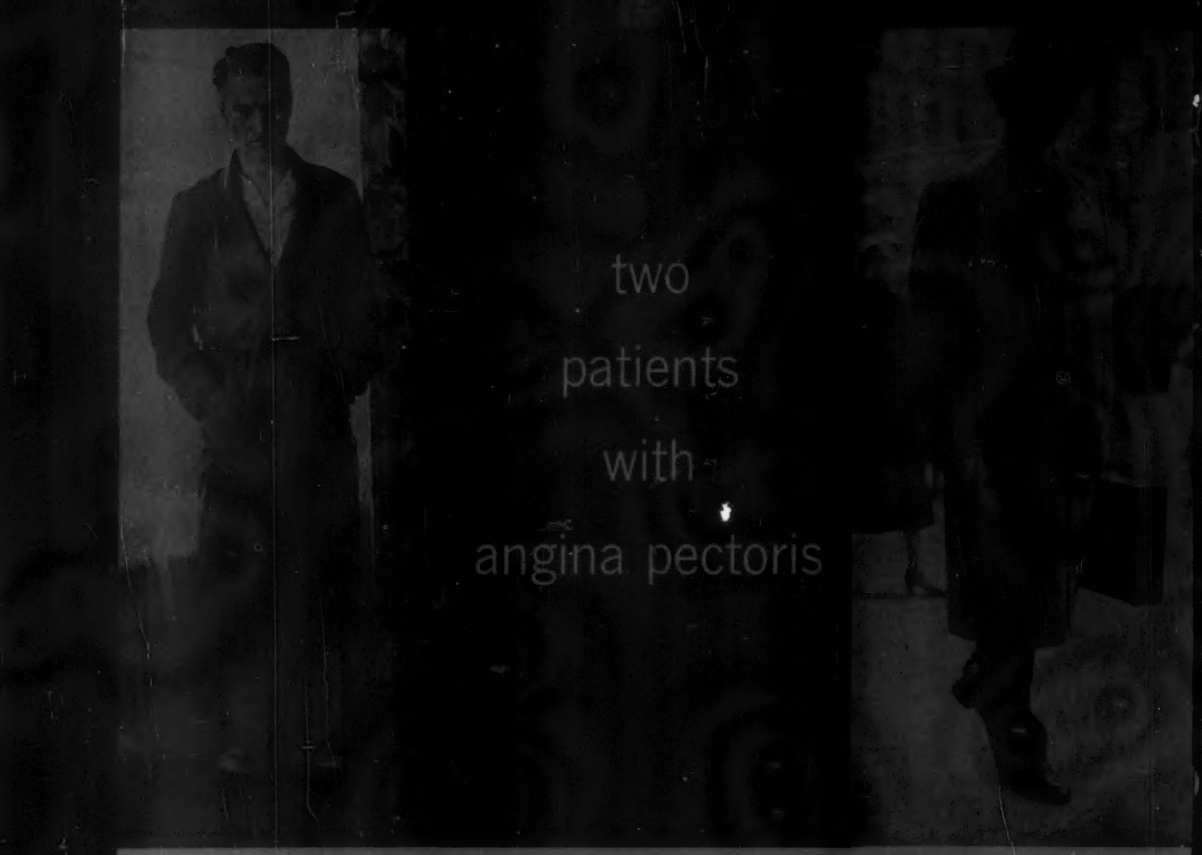

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References: 1. Rosenberg, H. N., and Michelson, A. L.: Am. J. M. Sc. 230:254 (Sept.) 1955. 2. Kory, R. C., *et al.*: Am. Heart J. 50:308 (Aug.) 1955. 3. Wilson, T., and Humphreys, P.: Angiology 3:1 (Feb.) 1953. 4. Plotz, M.: New York State J. Med. 52:2012 (Aug. 15) 1952. 5. Dailheu-Geoffroy, P.: L'Ouest-Médical, vol. 3 (July) 1950.

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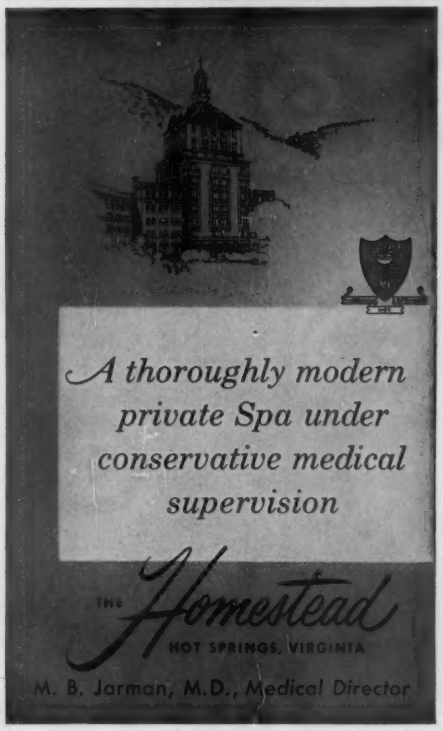
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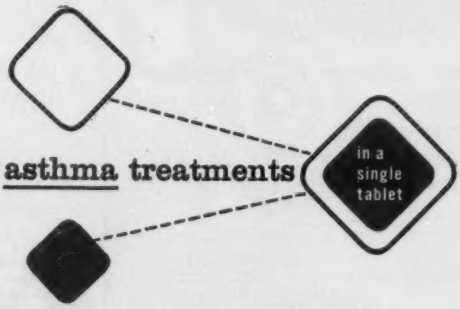

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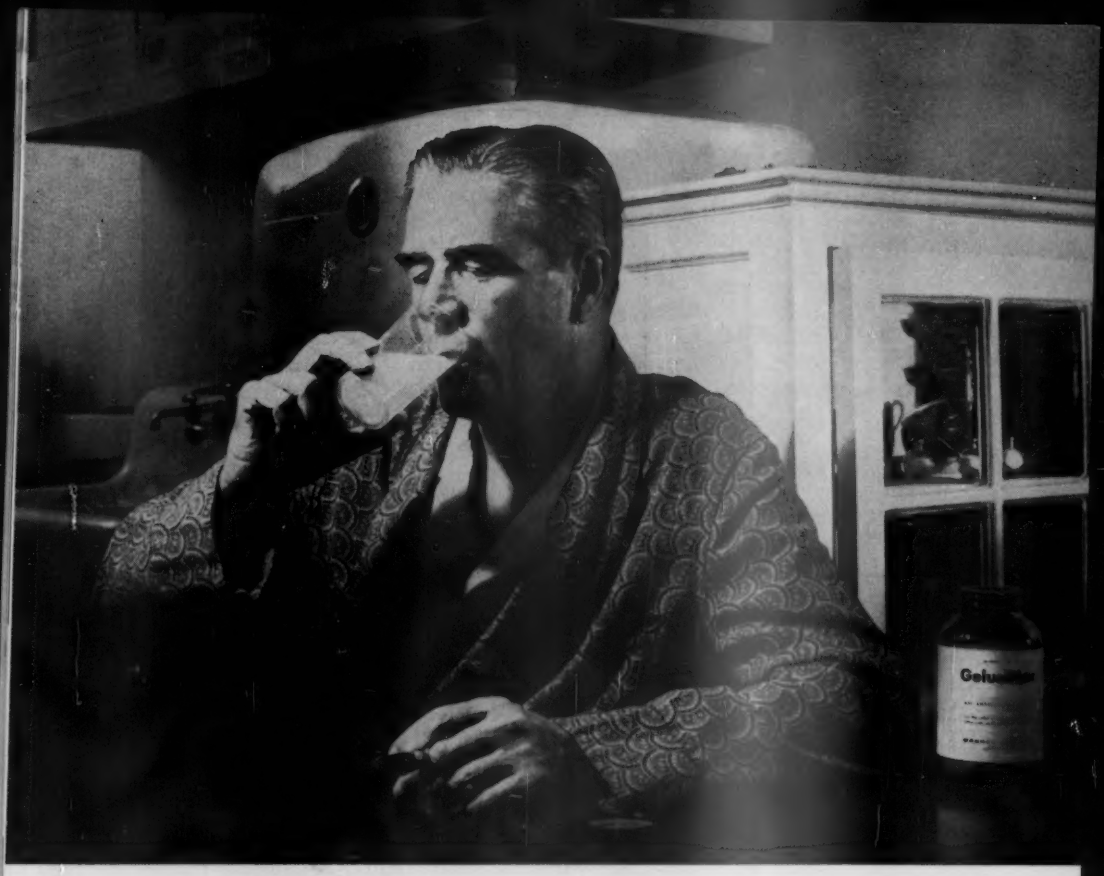

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References:

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3	50 mg.	25 mg.
4	50 mg.	50 mg.
5	75 mg.	50 mg.
6	75 mg.	75 mg.
7	100 mg.	75 mg.
8	100 mg.	100 mg.

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20	50 to 200 mg. daily	Blood pressure in 20 well controlled; reductions lasted twice as long as those induced by pentolinium. Each of 10 patients with previous experience with hexamethonium preferred Ecolid. Less difficulty with constipation; appetite improved; greater energy.	**	2
18	50 to 100 mg. daily	Hypertension in 18 well controlled. Supine blood pressure reduced without tachycardia. Constipation occurred infrequently.	Supine blood pressure lowered for 12 hours or more with single oral doses of 50 to 100 mg.	3,4
44	50 mg. daily	35 responded well; 14 of these became normotensive. All patients received reserpine as base therapy.	**	5
12	25 to 200 mg. daily	Blood pressure of all 12 satisfactorily controlled. Systolic blood pressure lowered average of 76 mm. Diastolic blood pressure lowered average of 42 mm.	**	6

*To date, a total of 63 investigators have reported on the use of Ecolid in more than 500 patients. They were practically unanimous in the opinion that Ecolid was highly effective. Nearly all commented on the prolonged duration of action—about 8 to 12 hours—which permitted a twice daily dosage schedule in most cases.

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2. Holbrook, W. P.: M. Clin. North America 39:405, 1955.
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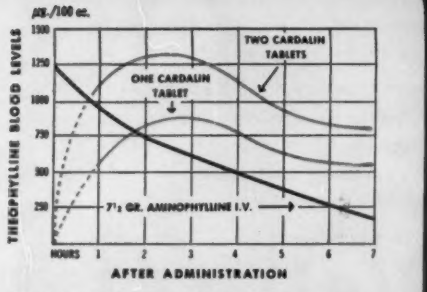

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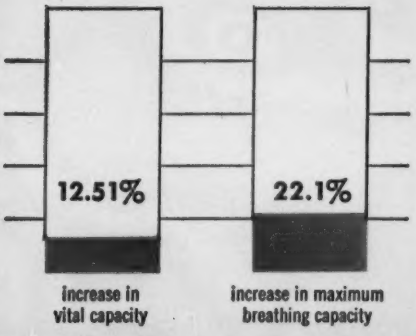

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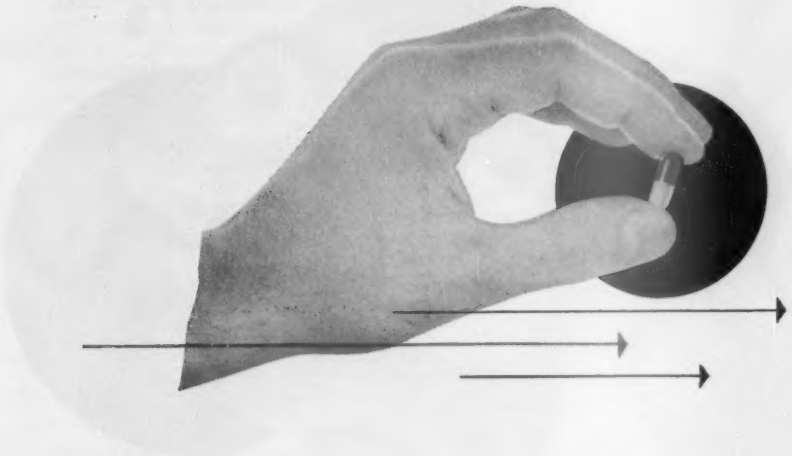

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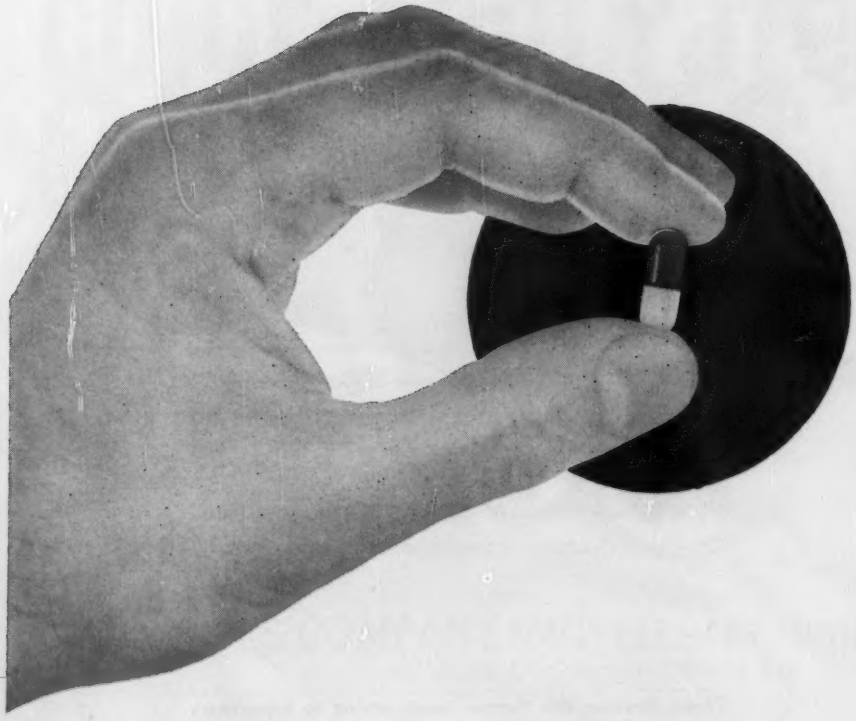

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REFERENCES:

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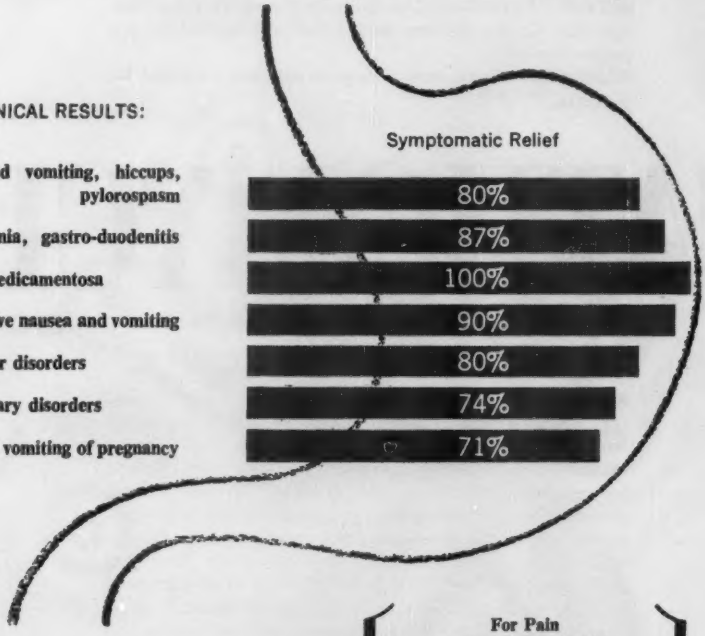

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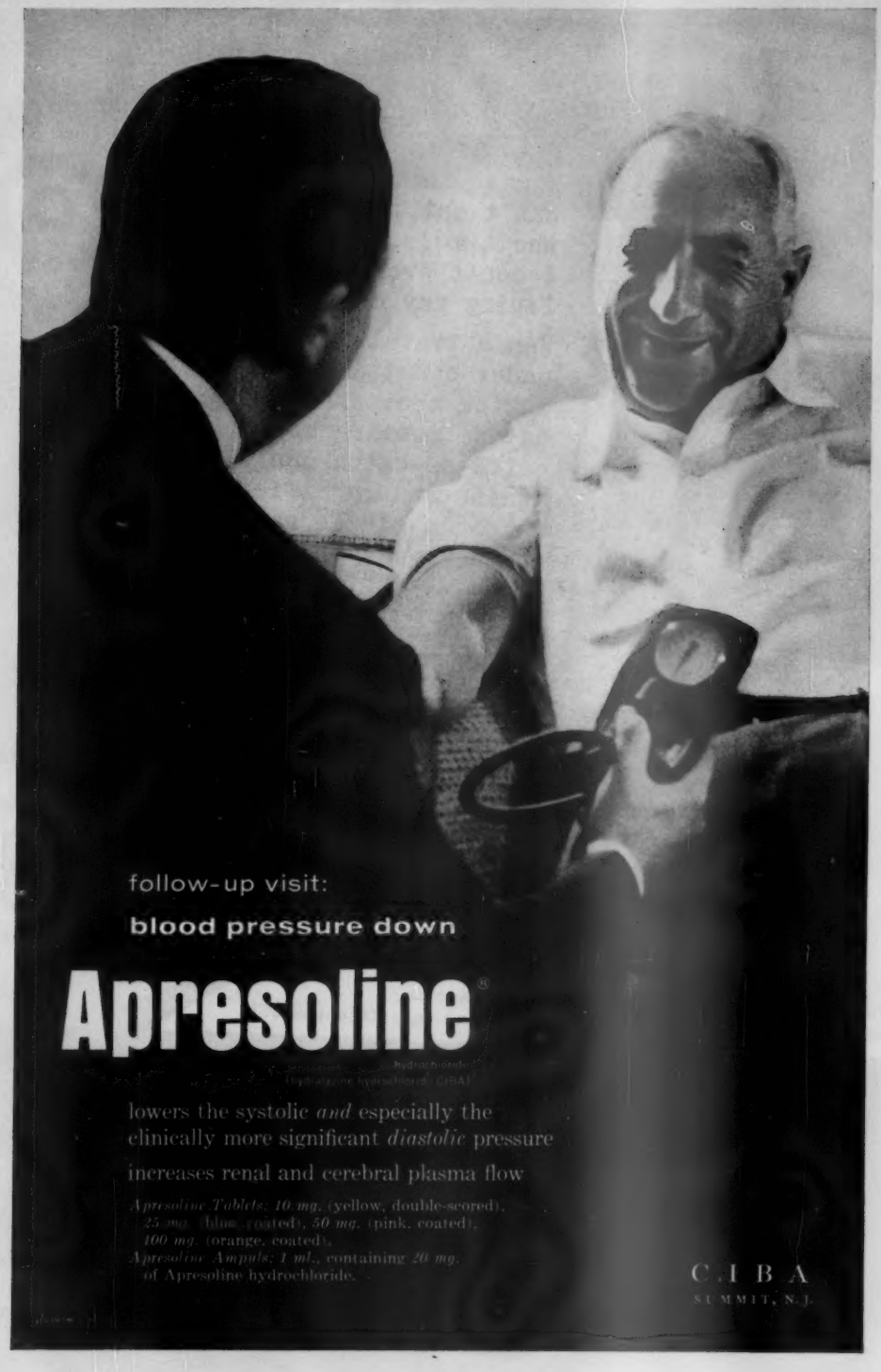
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CIBA
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Patient: "G.L., age 48, introduced himself to me as follows: 'Doctor, I'm so nervous I can't sleep... can't eat...gas bothers me all the time...everything's useless. I don't even want to make a living any more!'

"As a traveling salesman, he was under constant nervous pressure—making trains; keeping business dates; meeting schedules; eating catch-as-catch-can; sleeping on trains and in different hotels. He had a simple anxiety state—and obviously was deeply depressed."

Medication: 'Dexamyl' (S.K.F.)

Response: "His enthusiasm for 'Dexamyl' was unlimited: He said, '...it actually made life worth living again.'

"He is now able, for the first time in his life, to work with calmness and confidence."

(From a case history by the patient's physician; unposed photos of patient G.L. taken during an office visit.)

In the "business-man's syndrome" . . .

marked by nervousness, worry, tension,

and feelings of futility

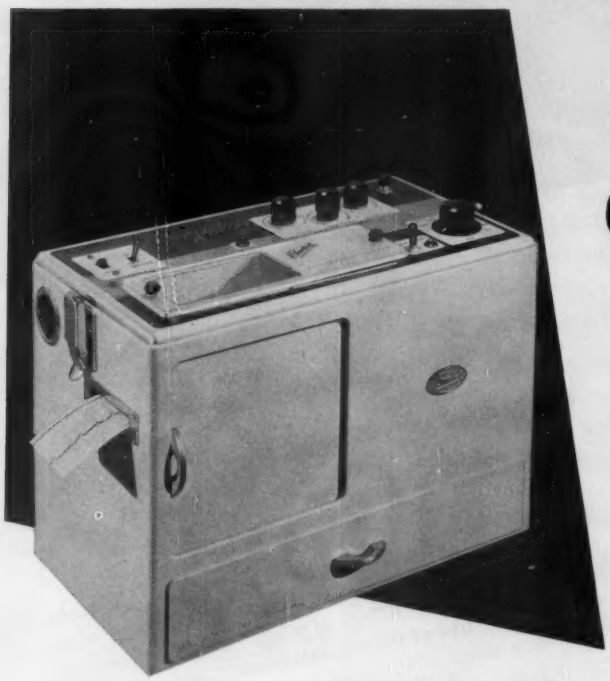
'Dexamyl'—a balanced combination of *two* mood-ameliorating components—provides a unique *normalizing* effect which is free of the dulling effects of many "anti-anxiety" agents alone; free of the excitation sometimes caused by stimulants alone.

Each 'Dexamyl' Tablet or teaspoonful (5 cc.) of the Elixir contains Dexedrine* (dextro-amphetamine sulfate, S.K.F.), 5 mg., and amobarbital, ½ gr.
Each 'Dexamyl' *Spansule* No. 1 gradually releases the equivalent of *two* tablets; each 'Dexamyl' *Spansule* No. 2 gradually releases the equivalent of *three* tablets.

DEXAMYL* | *tablets—elixir—*
Spansule† capsules

Smoothly and subtly relieves *both* anxiety and depression

Smith, Kline & French Laboratories, Philadelphia



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SUSPENSION CHLOROMYCETIN PALMITATE provides CHLOROMYCETIN (chloramphenicol, Parke-Davis) in a tempting, custard-flavored liquid form that youngsters take without cajoling or deception. Subsequent doses are swallowed as readily as the first, because SUSPENSION CHLOROMYCETIN PALMITATE leaves no unpleasant aftertaste and slides soothingly down the most irritated throat.

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CHLOROMYCETIN is a potent therapeutic agent and, because certain blood dyscrasias have been associated with its administration, it should not be used indiscriminately or for minor infections. Furthermore, as with certain other drugs, adequate blood studies should be made when the patient requires prolonged or intermittent therapy.

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Supplied: THIOMERIN Suppositories, boxes of 12. Injection THIOMERIN Solution, vials of 2 cc., boxes of 12; vials of 10 cc. Injection THIOMERIN (lyophilized), vials of 1.4 Gm. (10 cc. upon reconstitution) and 4.2 Gm. (30 cc. upon reconstitution).

1. Daly, J.W.: Am. J. M. Sc. *228*:440 (Oct.) 1954.

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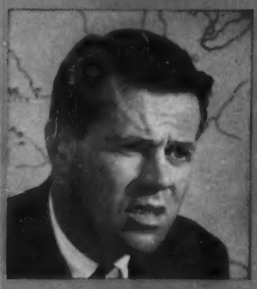

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He cannot tolerate an effective dose of veratrum alone.

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He cannot be controlled with rauwolfia or sedation alone.

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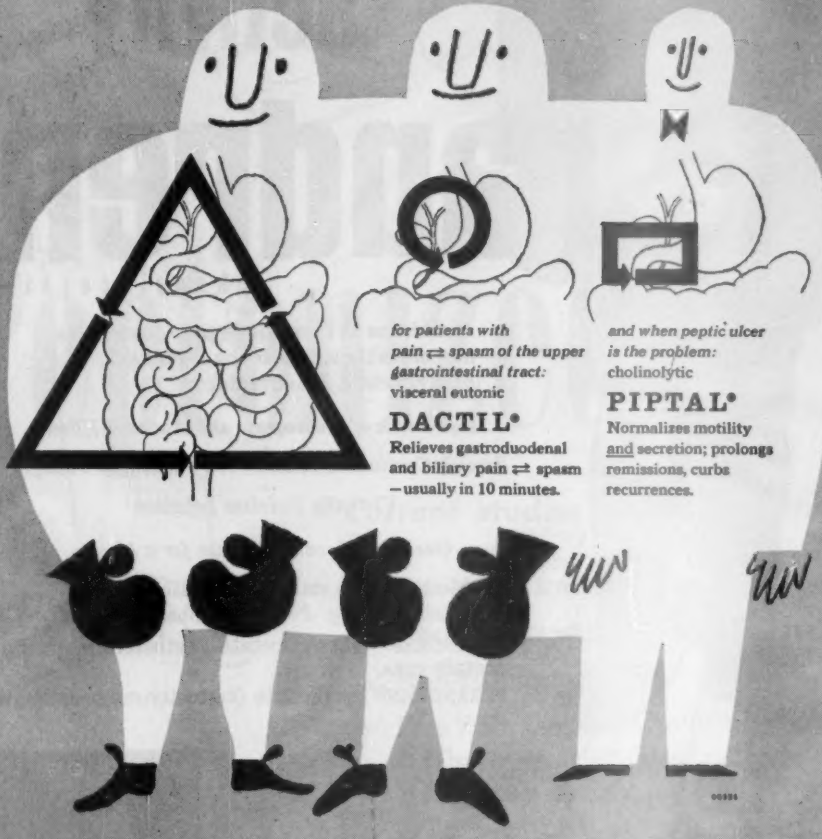

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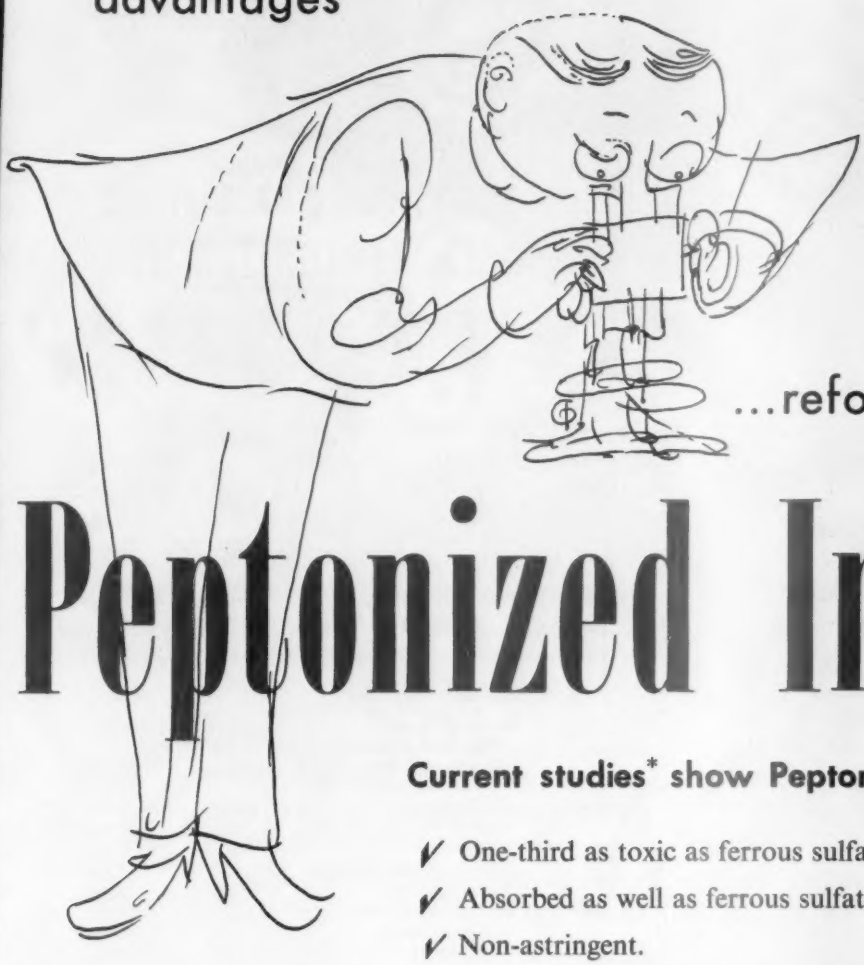

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Current studies* show Peptonized Iron—

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- ✓ More effective in iron-deficient anemias.

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*Keith, J. H.: Utilization and Toxicity of Peptonized Iron and Ferrous Sulfate, Read before the American Association for the Advancement of Science, Zoological Section, Atlanta, Georgia, December, 1955.

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The Livitamin formula, containing the B complex, provides integrated therapy to correct the blood picture, and to improve appetite and digestion.

Each fluidounce contains:

Iron peptonized (Equiv. in elemental iron to 71 mg.)	420 mg.
Manganese citrate, soluble	158 mg.
Thiamine hydrochloride	10 mg.
Riboflavin	10 mg.
Vitamin B_{12} (crystalline)	20 mcg.
Niacinamide	50 mg.
Pyridoxine hydrochloride	1 mg.
Pantothenic acid	5 mg.
Liver fraction 1	2 Gm.
Rice bran extract	1 Gm.
Inositol	30 mg.
Choline	60 mg.

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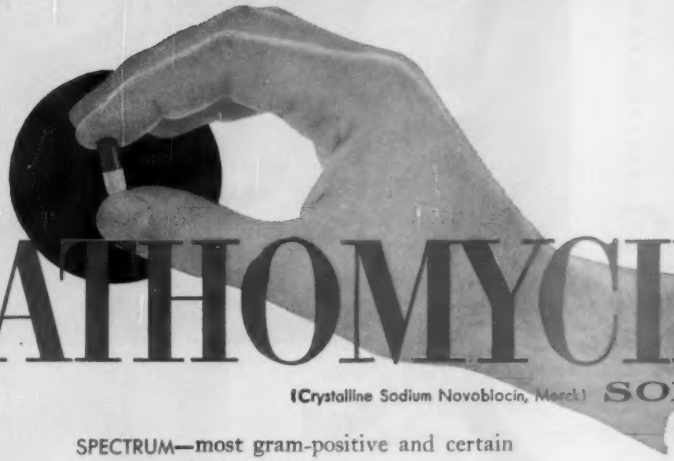

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SPECTRUM—most gram-positive and certain gram-negative pathogens.

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SUPPLIED—250 mg. capsules of 'CATHOMYCIN', bottles of 16.

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Restful nights are added to calm days for anxiety and mild hypertension patients when you prescribe Nembu-Serpin. The 30 mg. (½ gr.) of short-acting Nembutal (Pentobarbital Calcium) in each tiny Filmtab quickly induces drowsiness at bedtime, followed by refreshing sleep. Then the 0.25 mg. of longer-acting reserpine in each Filmtab calms patients all through the following days.

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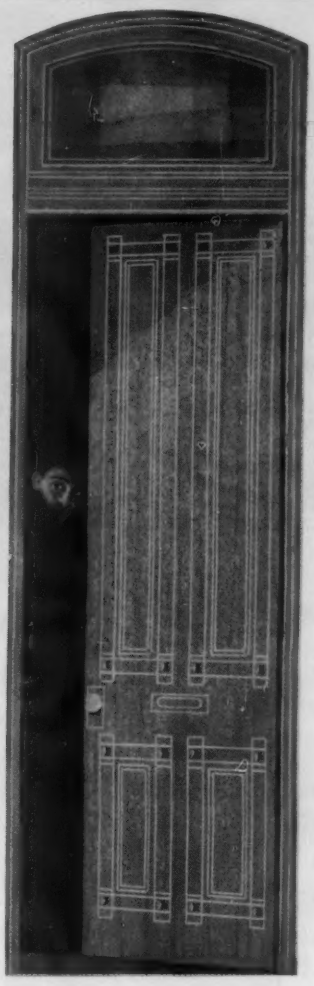

'Thorazine' relieved this patient's anxiety, tension and fear and made it possible for him to return to work.

'THORAZINE' CASE REPORT

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This case report is from the files of a general practitioner.

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Available in ampuls, tablets and syrup (as the hydrochloride), and in suppositories (as the base).

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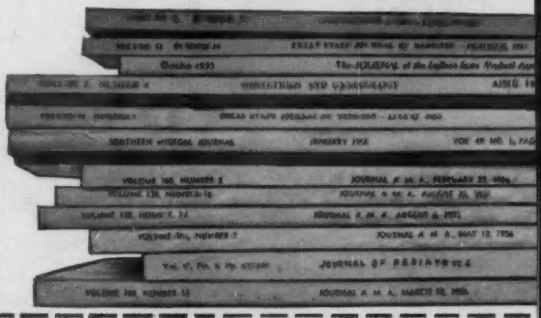

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Your own results will show why "The bibliography specifies RONCOVITE."

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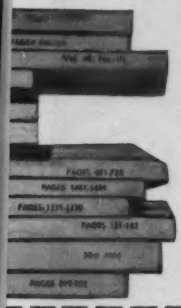

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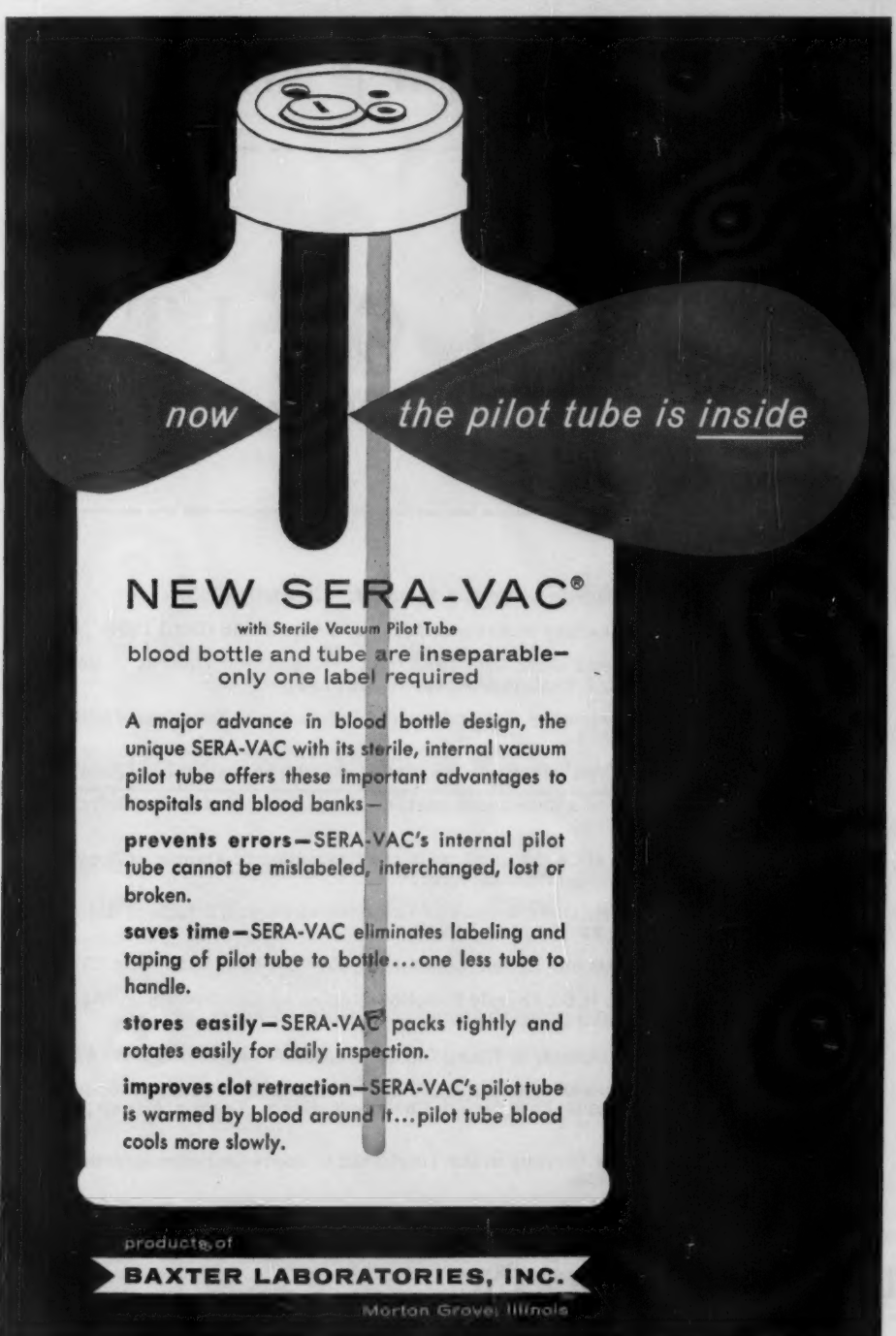
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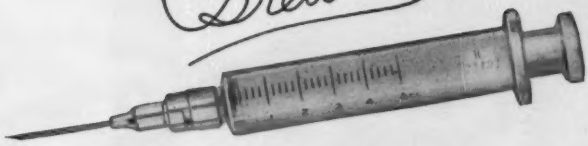

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1. Sturnick, M. I.; Riseman, J. E. F.; and Sagall, E. I.: Studies on the Action of Quinidine in Man: J. A. M. A. 121; 917 (March 20) 1943
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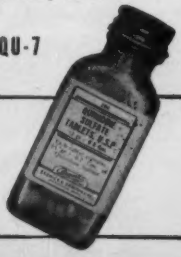

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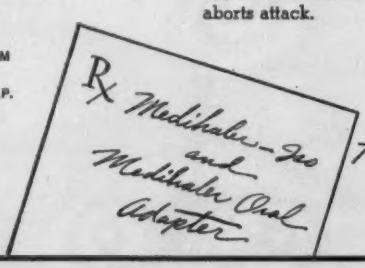
0.25% solution of isoproterenol HCl U.S.P.

On your prescription be sure to write "Medihaler-Iso (or Medihaler-Epi) AND Medihaler Oral Adapter," since medication cannot be used without Adapter. For refills write for medication only.



Another First from
Riker LOS ANGELES

PHEOCHROMOCYTOMA?

confirmed
or
denied
simply, specifically

Regitine®

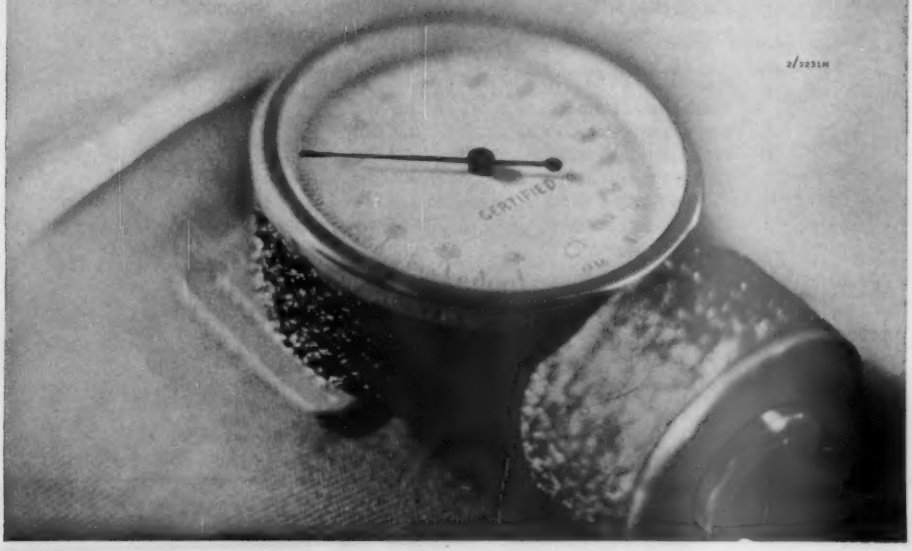
Readily performed in the office unassisted, the reliable diagnostic test for pheochromocytoma with Regitine should be routine in hypertension. Potent antiadrenergic, Regitine is also valuable therapeutically in hypertensive crises and in peripheral vascular disease. Explanatory booklet is available from your CIBA representative or the Medical Service Division.

Supplied: *Ampuls* (for intramuscular or intravenous use in diagnosis), each containing 5.0 mg. Regitine methanesulfonate in lyophilized form. *Tablets* for oral administration (white, scored), each containing 50 mg. Regitine hydrochloride.

Regitine® methanesulfonate (phentolamine methanesulfonate CIBA)
Regitine® hydrochloride (phentolamine hydrochloride CIBA)

CIBA
SUMMIT, N.J.

2/2231M



a "judicious combination..."

for antiarthritic therapy

SALCORT*

That cortisone and the salicylates have a complementary action has been well established.[1-5] In rheumatic conditions, functional improvement and a sense of feeling well are noted early. No withdrawal reactions have been reported.

One clinician states: "By a judicious combination of the two agents . . . it has been possible to bring about a much more favorable reaction in arthritis than with either alone. Salicylate potentiates the greatly reduced amount of cortisone present so that its full effect is brought out without evoking undesirable side reactions."[1]

INDICATIONS:

Rheumatoid arthritis . . . Rheumatoid spondylitis . . . Rheumatic fever . . . Bursitis . . . Still's disease . . . Neuromuscular affections

EACH TABLET CONTAINS:

Cortisone acetate	2.5 mg.
Sodium salicylate	0.3 Gm.
Aluminum hydroxide gel, dried	0.12 Gm.
Calcium ascorbate (equivalent to 50 mg. ascorbic acid)	60 mg.
Calcium carbonate	60 mg.

* U.S. Pat. 2,691,662

1. Busse, E.A.: Treatment of Rheumatoid Arthritis by a Combination of Cortisone and Salicylates. Clinical Med. 11:1105 (Nov., 1955).
2. Roskam, J., VanCawenberge, H.: Abst. in J.A.M.A., 151:248 (1953).
3. Coventry, M.D.: Proc. Staff Meet., Mayo Clinic, 29:60 (1954).
4. Holt, K.S., et al.: Lancet, 2:1144 (1954).
5. Spies, T.D., et al.: J.A.M.A., 159:645 (Oct. 15, 1955).

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NEW YORK
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The S. E. Massengill company

Hypotensive action without side effects

RENIR

Reserpine with a safety factor

The desirable hypotensive action of reserpine is often accompanied by distressing side effects. These include nasal congestion, hyperperistalsis, nightmares and mental depression.

Renir, which provides the desired action of reserpine, counterbalanced by the well-known effects of ephedrine, offers the optimum in hypotensive therapy. Untoward reactions are minimized, and tranquilization is maintained.

Investigators state that: "... with reserpine and ephedrine, the untoward effects of each are counteracted and the desirable effects of each are enhanced."[1]

INDICATIONS: In the treatment of mild, moderate and labile hypertension. Also anxiety and tension states; mild to severe neurosis.

SUGGESTED DOSAGE: For hypertension, 1 to 3 tablets daily. As a tranquilizer in mentally disturbed states, 2 to 4 tablets daily.

SUPPLIED: Tablets containing reserpine 0.25 mg., and ephedrine 8.0 mg., in bottles of 100.

CONTRAINDICATIONS: To be used with caution in patients with peptic ulcer, mental depression, cardiac conditions and related disorders.

LITERATURE AND SAMPLES ON REQUEST.

1. *Feinblatt, T.M., Feinblatt, H.M., and Ferguson, E.A.: Rauwolfia-Ephedrine, A Superior Hypotensive-Tranquilizer. In press.*

THE S. E. MASSENGILL COMPANY

Bristol, Tennessee

New York • Kansas City • San Francisco

Enriched Bread... and Child Health in America

The enrichment of commercial white bread with thiamine, riboflavin, niacin, and iron is one of the important factors in the improvement of nutrition in America's school children.[1] Improved nutrition appears to have made a valuable contribution to the improvement of child health during recent years.[2]

Containing nonfat milk solids (usually 4 lbs. per 100 lbs. of flour) as well as officially defined amounts of B vitamins and iron, enriched bread provides high percentages of recommended daily dietary allowances for children.

The protein of enriched bread, an aggregate of flour, milk, and yeast proteins, is high in nutritive quality, effective for growth as well as tissue maintenance. On the basis of its percentage of calories provided, enriched bread supplies substantially more than its share of niacin, thiamine, and iron, and a goodly proportion of riboflavin and calcium. Because enriched bread presents carbohydrate and good quality protein simultaneously, the carbohydrate thereby "sparing" protein, it helps promote optimum protein anabolism.[3] For all these reasons, enriched bread constitutes a valuable asset to good nutritional health in children.

1. Bowes, A. deP.: Dietotherapy—Nutrition of Children During Their School Years, Am. J. Clin. Nutrition 3: 254 (May-June) 1955.
2. Kelly, H. T.: Impact of Modern Nutrition on Twentieth Century Morbidity, Pennsylvania M. J. 58: 481 (May) 1955.
3. Cantarow, A., and Trumper, M.: Clinical Biochemistry, ed. 5, Philadelphia, W. B. Saunders Company, 1955, pp. 139, 140.

Percentages of Recommended Daily Dietary Allowances* for Children Provided by Enriched Bread—6 and 8 slices

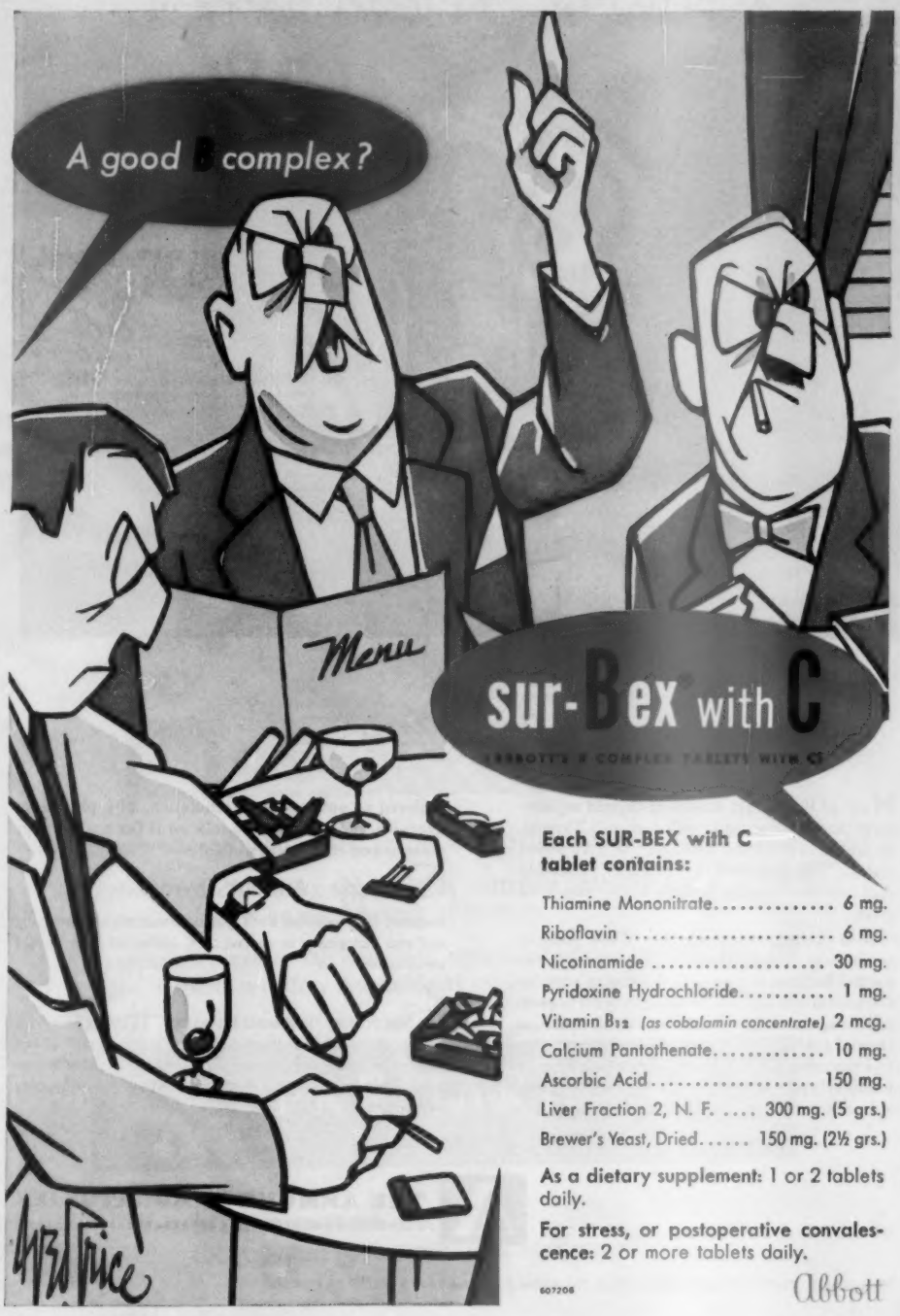
	Children Ages 4 to 6 years		Children Ages 7 to 9 years	
	6 slices	8 slices	6 slices	8 slices
Protein	23%	31%	20%	26%
Niacin	38	50	30	40
Riboflavin	18	23	14	19
Thiamine	41	55	33	44
Calcium	12	16	12	16
Iron	41	55	33	44
Calories	24	32	19	25

*National Research Council's recommended daily dietary allowances (1953):
Children, 4 to 6 years of age; weight, 40 lbs.; height, 43 inches.
Children, 7 to 9 years of age; weight, 59 lbs.; height, 51 inches.

AMERICAN BAKERS ASSOCIATION

20 NORTH WACKER DRIVE • CHICAGO 6, ILLINOIS

The nutritional statements made in this advertisement have been reviewed by the Council on Foods and Nutrition of the American Medical Association and found consistent with current authoritative medical opinion.



Each SUR-BEX with C tablet contains:

Thiamine Mononitrate	6 mg.
Riboflavin	6 mg.
Nicotinamide	30 mg.
Pyridoxine Hydrochloride	1 mg.
Vitamin B_{12} *(as cobalamin concentrate)*	2 mcg.
Calcium Pantothenate	10 mg.
Ascorbic Acid	150 mg.
Liver Fraction 2, N. F.	300 mg. (5 grs.)
Brewer's Yeast, Dried	150 mg. (2½ grs.)

As a dietary supplement: 1 or 2 tablets daily.

For stress, or postoperative convalescence: 2 or more tablets daily.

607208

Abbott

The Thyroid Gland

Many of the earliest studies of thyroid replacement therapy were made with Armour's Thyroid. In fact, a well-known textbook* of that period states: "The desiccated thyroid gland, preferably that manufactured by Armour & Co., should be given . . ."

With the tremendous supplies of raw material available to Armour Research Laboratories, it was natural for them to pioneer in developing superior methods of selection and blending in order to overcome seasonal and geographic variations in animal thyroid potency. Such methods are in use today and represent the first control step which Armour is uniquely able to exercise over the finished product—one more reason why Armour Thyroid has achieved so outstanding a reputation, why physicians everywhere have come to rely on it for uniformity, potency and effectiveness.

Specify Armour Thyroid—

Prepared from selected fresh glands, standardized chemically and also biologically to contain 0.2% iodine U.S.P. in thyroid combination.

or

The New Premier "Isothermic Processed" thyrar®—

Exclusive use of beef thyroid glands, "quick-frozen" at the time of removal, and "isothermic processing" provide a new thyroid preparation of U.S.P. strength notable for high purity and uniformity.

THE ARMOUR LABORATORIES
A DIVISION OF ARMOUR AND COMPANY · KANKAKEE, ILLINOIS

*Richardson, H.: The Thyroid and Parathyroid Glands, Philadelphia, P. Blakiston's Sons & Co., 1905, pp. 9 and 197.

A "SENSE OF WELL-BEING" IS A WOMAN'S PRIVILEGE

Every woman who suffers in the menopause deserves "Premarin."

Relief from distressing symptoms is promptly obtained and a "sense of well-being" is an extra benefit of therapy.

"Premarin" presents the complete equine estrogen-complex. Has no odor, imparts no odor. Available as tablets or liquid.

"PREMARIN"®
Conjugated estrogens (equine)

in the menopause and the pre- and postmenopausal syndrome

Ayerst AYERST LABORATORIES • New York, N. Y. • Montreal, Canada

5644

Relaxed but awake

In emotional and nervous disorders, Mebaral exerts its calming influence without excessive hypnotic action.

Mebaral is also a reliable anticonvulsant.

INDICATIONS:

Because of its high degree of sedative effectiveness, Mebaral finds a great field of usefulness in the regulation of agitated, depressed or anxiety states, as well as in convulsive disturbances. Specific disorders in which the calming influence of Mebaral is indicated include neuroses, mild psychoses, nervous symptoms of the menopause, hypertension, hyperthyroidism and epilepsy.

for sedation

Mebaral®

Tasteless **TABLETS**

Sedative:
32 mg. (½ grain) and new 50 mg. (¾ grain)

Antiepileptic:
0.1 Gm. (1½ grains) and 0.2 Gm. (3 grains)

WINTHROP LABORATORIES New York 18, N.Y., Windsor, Ont.

Mebaral, trademark reg. U. S. & Canada, brand of mephobarbital

most convenient
digitalis
preparation...
change route
any time
without changing
dose or interval

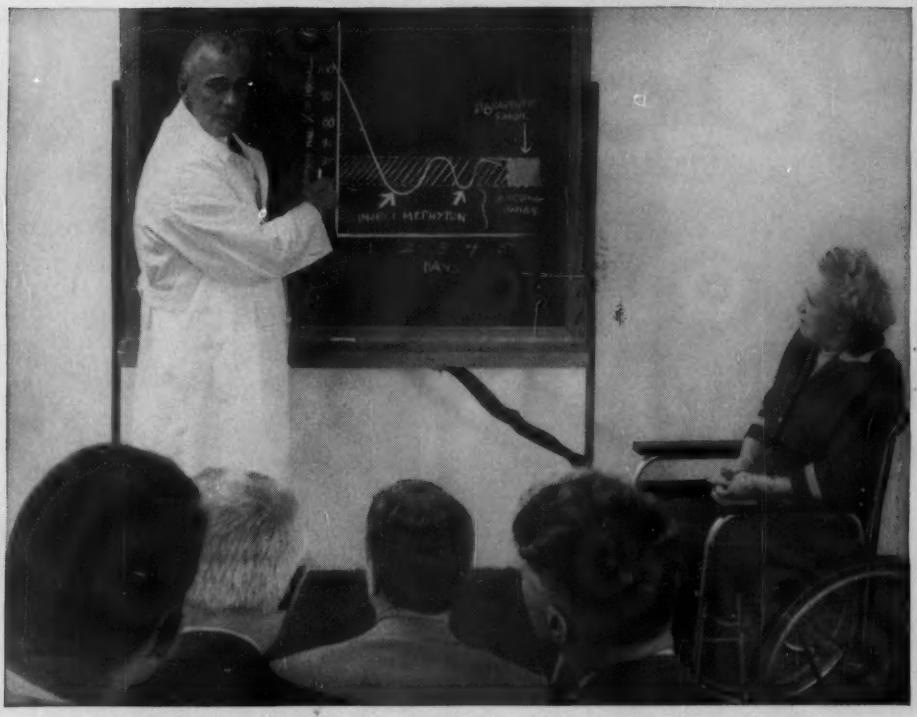
DIGITALINE NATIVELLE

Now with Digitaline Nativelle Intramuscular, a complete range of routes of administration is available. This preparation—specifically designed for I.M. use—avoids irritation often encountered when I.V. forms are administered intramuscularly. The dosage schedule with DIGITALINE NATIVELLE need never be changed because of change in the route of administration. The same advantages are provided by all forms, enabling the physician to cope with any change in the patient's status. Prescribe DIGITALINE NATIVELLE—the original pure crystalline digitoxin • pure active principle • complete absorption • rapid onset of action • smooth, even maintenance • frequent dosage readjustment unnecessary • virtual freedom from gastric upset

Consult your Physicians' Desk Reference for dosage information.

VARICK Pharmacal Company, Inc.
(Division of E. Fougera & Co., Inc.)
75 Varick Street, New York 13, N. Y.

adjusts anticoagulant-depressed prothrombin time



MAJOR ADVANTAGES: Action detectable within 15 minutes, prothrombin time normalized within 4 to 12 hours, bleeding checked in 3 to 6 hours.

EMULSION OF Mephyton®
(VITAMIN K_1 INJECTION, MERCK)

"It is shown that oil-soluble vitamin K_1 is more effective than any other agent now available in combating drug-induced hypoprothrombinemia."[1] However, the usefulness of Mephyton lies not only in overcoming bleeding emergencies, but also in adjusting upwards to safe therapeutic levels unduly prolonged prothrombin times. Mephyton permits the clinician to do this easily and without gross changes in the regular anticoagulant dosage. . . ."no untoward effects have been observed to follow the administration of vitamin K_1."[1]

INDICATIONS: Hypoprothrombinemia due to Dicumarol®, Cumopyran®, Tromexan®, Hedulin®, 'Dipaxin', warfarin and other phenylindanediones; also when due to antibiotics, salicylates, obstructive jaundice, hepatic disease, and impaired gastrointestinal absorption.

SUPPLIED: In boxes of six 1-cc. ampuls, 50 mg. of vitamin K_1 per cc.

1. Gamble, J. R., *et al.*, *Arch. Int. Med.* 95:52, January 1955.

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DIVISION OF MERCK & CO., INC.

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PLANS...

for diarrhea control

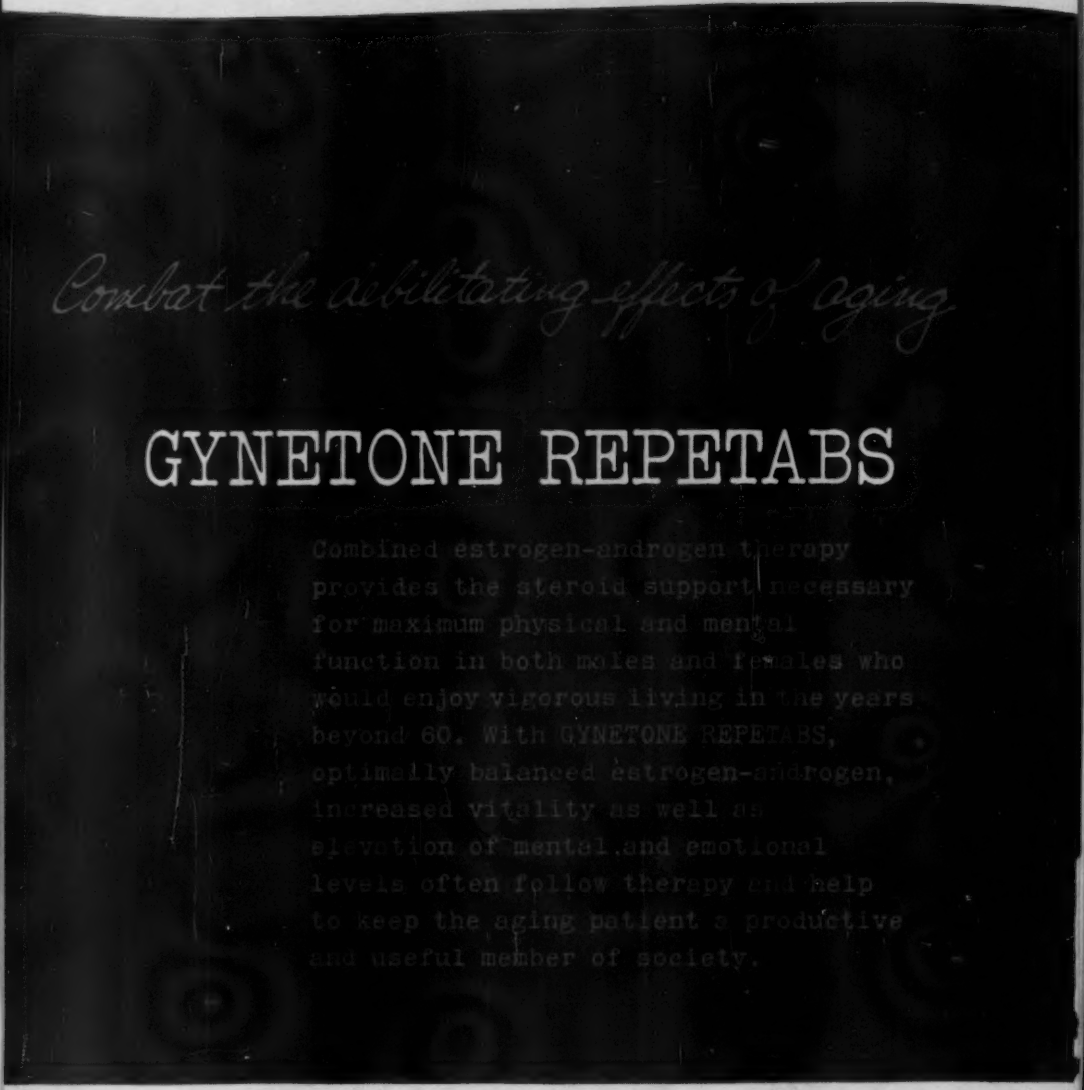
Diarrhea attacks without warning. For the management of susceptible *infectious* forms, STREPTOMAGMA combines potent antibacterial, adsorptive, and protective actions. Soothes the irritated bowel, promotes development of well-formed stools. For routine management of common *noninfectious* diarrhea, prescribe KALPEC®—pectin with kaolin in alumina gel.

Supplied: STREPTOMAGMA, bottles of 3 fl. oz. and 1 pint.
KALPEC, bottles of 12 fl. oz.

STREPTOMAGMA®

Dihydrostreptomycin Sulfate and Pectin with Kaolin in Alumina Gel

Base Map © by Rand McNally & Co., R.L. 56Y105


Combat the debilitating effects of aging
GYNETONE REPETABS
Combined estrogen-androgen therapy provides the steroid support necessary for maximum physical and mental function in both males and females who would enjoy vigorous living in the years beyond 60. With GYNETONE REPETABS, optimally balanced estrogen-androgen, increased vitality as well as elevation of mental and emotional levels often follow therapy and help to keep the aging patient a productive and useful member of society.

also valuable in: osteoporosis • protein depletion • menopause

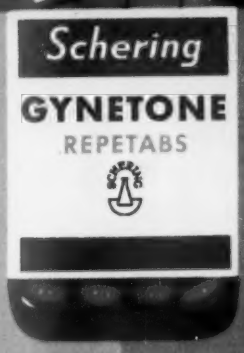
two strengths for individualized therapy

GYNETONE REPETABS ".02": Ethinyl Estradiol U.S.P. 0.02 mg. plus 5 mg. Methyltestosterone U.S.P.
GYNETONE REPETABS ".04": Ethinyl Estradiol U.S.P. 0.04 mg. plus 10 mg. Methyltestosterone U.S.P.

GYNETONE,® combined estrogen-androgen.
REPETABS,® Repeat Action Tablets. 67-J-63-256

unchanged life

in the changing years



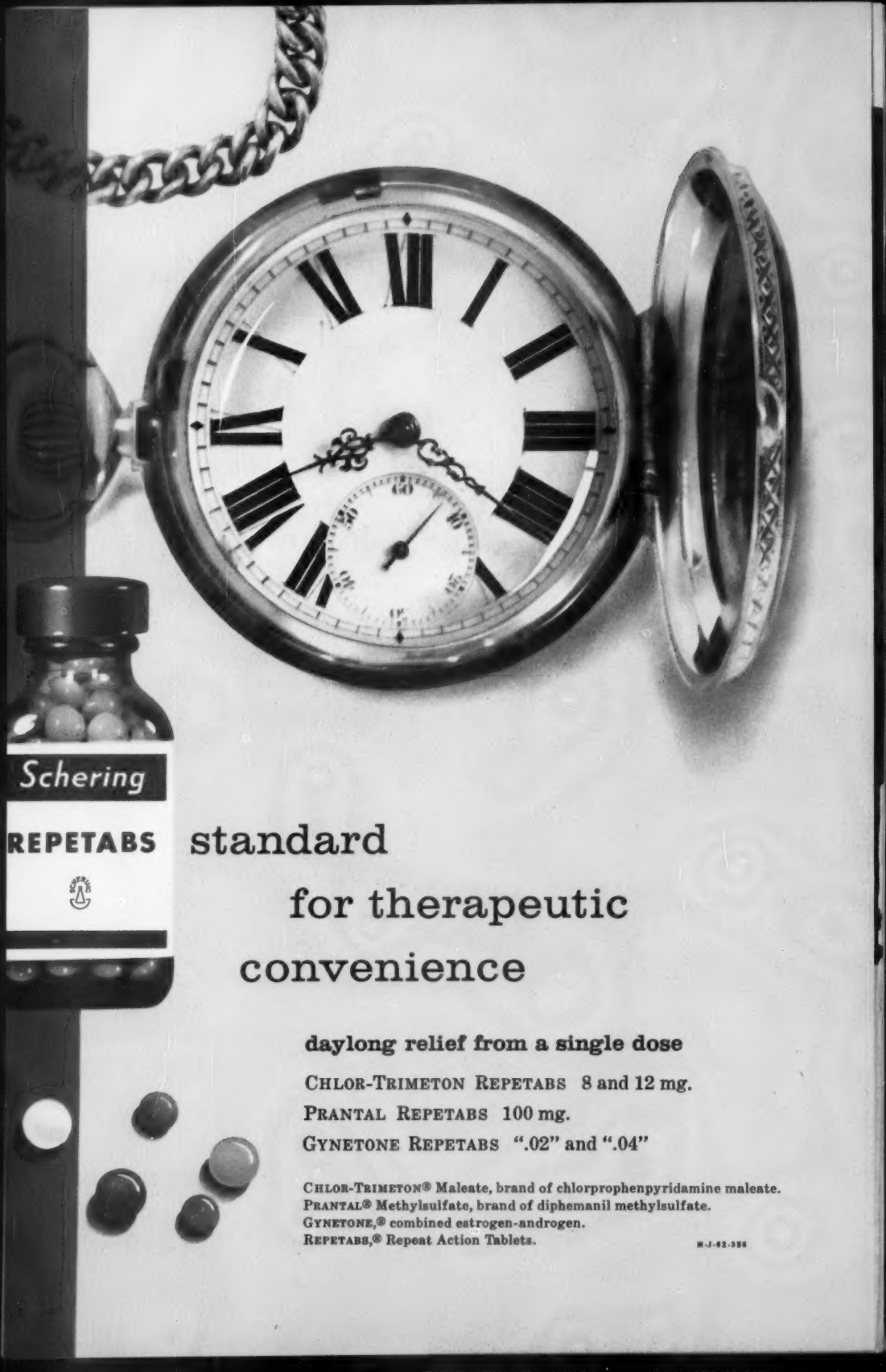
two strengths

0.02 mg. ethinyl estradiol plus 5 mg. Methyltestosterone U.S.P.

0.04 mg. ethinyl estradiol plus 10 mg. Methyltestosterone U.S.P.

GYNETONE,® combined estrogen-androgen.

REPETABS,® Repeat Action Tablets. 67-J-61-256



standard for therapeutic convenience

daylong relief from a single dose

CHLOR-TRIMETON REPETABS 8 and 12 mg.

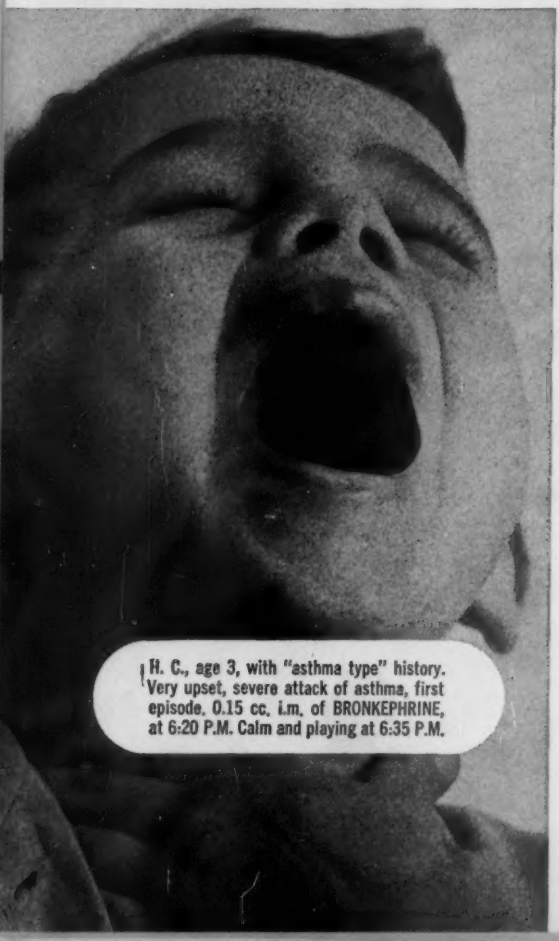
PRANTAL REPETABS 100 mg.

GYNETONE REPETABS ".02" and ".04"

CHLOR-TRIMETON® Maleate, brand of chlorprophenpyridamine maleate.
PRANTAL® Methylsulfate, brand of diphemanil methylsulfate.
GYNETONE,® combined estrogen-androgen.
REPETABS,® Repeat Action Tablets.

M-J-62-386

air and reassurance



H. C., age 3, with "asthma type" history. Very upset, severe attack of asthma, first episode. 0.15 cc. i.m. of BRONKEPHRINE, at 6:20 P.M. Calm and playing at 6:35 P.M.

Fright, as well as anoxia, grasps the classical "first-attack" asthmatic child. You well know that this youngster needs air and reassurance. Both are available with BRONKEPHRINE without side effects subtracting from success. BRONKEPHRINE's lack of excitation,[1,2,3] in fact, far less than epinephrine,[3] has been particularly valuable in the control of asthma in children.[1] This can be true in your practice, too. BRONKEPHRINE's lack of excitation is reflected by another happy advantage—lack of pressor effect.[1,3-6] Even hypertensive asthmatics can now receive *potent* antiasthmatic therapy without affecting their blood pressure—a factor of major importance in selecting asthma therapy—whether the patient is hypertensive or not.

But this potent drug, "...a superior tool for the treatment of bronchial asthma,"[1] unlike other effective sympathomimetic amines, develops tolerance far less frequently and to a lesser degree—an obvious advantage in the prolonged treatment of asthma.[1]

BRONKEPHRINE (ethylnorepinephrine Breon) for either intramuscular or intravenous injection—your drug of choice for *any* asthmatic—is available in 10 cc. multidose vials, containing 2 mg. of BRONKEPHRINE in each cc.

Bronkephrine®

(ETHYLNOREPINEPHRINE BREON)

another exclusive, quality-controlled parenteral from Breon, your House of Advanced Office Parenteral Medication.

We will be pleased to send you more information, or a clinical sample for your practice. GEORGE A. BREON & COMPANY
1450 Broadway, New York 18, N. Y.

1. Foland, J. P.: Postgrad. Med. 18:397, 1955.
2. Schulte, J. W.; Reif, E. C.; Bacher, J. A.; Lawrence, W. S., and Tainter, M. L.: J. Pharmacol. & Exper. Therap. 71:62, 1941.
3. Bubert, H. M., and Doenges, J. P.: Bull. School Med. Univ. Maryland 31 (No. 1), 1946.
4. Tainter, M. L.; Pedden, J. R., and James, M.: J. Pharmacol. & Exper. Therap. 51:371, 1934.
5. Pedden, J. R.; Tainter, M. L., and Cameron, W. M.: J. Pharmacol. & Exper. Therap. 55:242, 1935.
6. Hartman, M. M.: Ann. Allergy 3:366, 1945.

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To counteract extremes of

mood... **Desbutal®**

(DESOXYN® plus NEMBUTAL®)

Desbutal dispels your patient's depression, anxiety. One capsule represents 5 mg. DESOXYN Hydrochloride (Methamphetamine Hydrochloride, Abbott), and 30 mg. NEMBUTAL Sodium (Pentobarbital Sodium, Abbott). Bottles of 100 and 1000. Abbott

KEY

the around the clock protector in ANGINA

NITROGLYN®

(SUSTAINED ACTION NITROGLYCERIN)

..."Has been proven effective in the treatment and prevention of angina pectoris attacks. . . The effect . . sets in very quickly and lasts for a very long time . . ."[1]

. . "In summary, the agent seems to be quite effective and seems to be devoid of harmful side effects even when continued over long periods of time . . ."[2]

. . "A highly useful preparation of slow release nitroglycerin . . ."[3]

. . ."Results in alleviation of the angina in a significantly high percentage of cases."[4]

NITROGLYN tablets are available in two dosage forms, gr. 1/25th and gr. 1/10th.

Literature and samples available on request.

KEY CORPORATION
MIAMI 37, FLORIDA

References:

1. **HUEBER, E. F., M.D.; et al.,** *Wiener Klinische Wochenschrift, Vienna, Austria, May, 1955 (1st University Medical Clinic)*

2. **BOYD, L. J., M.D.,** *Director of Medicine, New York Medical College; Flower & Fifth Avenue Hospital, N. Y. C.; personal communication*

3. **PLOTZ, MILTON, M.D., N.Y.C.;** *personal communication*

4. **EICHERT, HERBERT, M.D.;** *Chief Cardiology Section, Jackson Memorial Hospital, Miami, Fla.; personal communication*

NEW PRODUCT

"THIOSULFIL"® -A

Brand of sulfamethizole with phenylazo-diamino-pyridine HCl

in urinary tract infections

when analgesia is desired

Combines

"Thiosulfil," single sulfonamide specifically for urinary tract infections

and

phenylazo-diamino-pyridine HCl for prompt and penetrating local analgesic effect.

Provides

Potent bacteriostatic action at the site of infection with rapid relief of pain and discomfort.

Each tablet contains 0.25 Gm. of sulfamethylthiadiazole and 50 mg. of phenylazo-diamino-pyridine HCl — No. 784 — bottles of 100 and 1,000.

Suggested dosage: 2 tablets, four times daily.

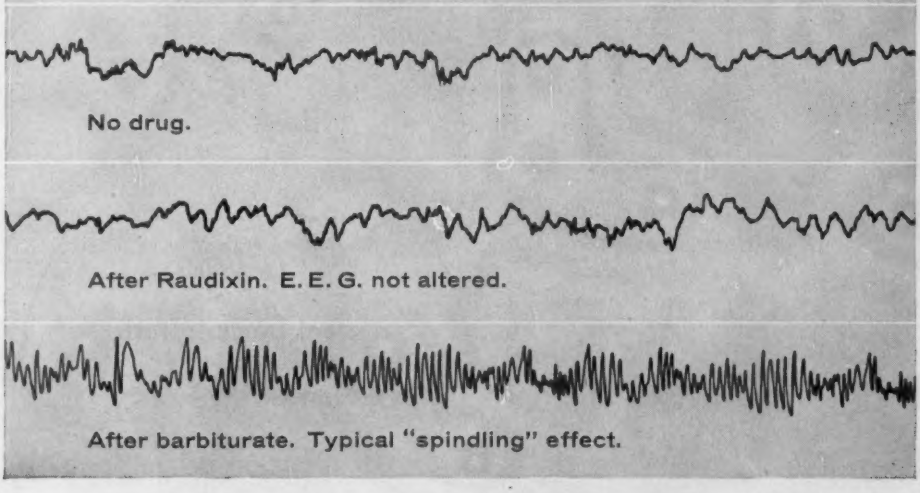
Also available: "Thiosulfil" Tablets and Suspension, 0.25 Gm. per tablet or per 5 cc.

5674

Ayerst Laboratories Ayerst New York, N. Y. • Montreal, Canada

WHAT IS THE DIFFERENCE BETWEEN A TRANQUILIZER AND A SEDATIVE?

Comparison of the effect of Raudixin (tranquilizer) and a barbiturate (sedative) on the cortical electroencephalogram



Because barbiturates and other sedatives depress the cerebral cortex, the sedation achieved is accompanied by a reduction in mental alertness.

Raudixin acts in the area of the midbrain and diencephalon, and does not depress the cerebral cortex. Consequently, the tranquilizing (ataractic) effect achieved is generally free of loss of alertness.

RAUDIXIN

Squibb Whole Root Rauwolfia Serpentina

DOSAGE: 100 mg. b.i.d. initially; may be adjusted within a range of 50 mg. to 500 mg. daily. Most patients can be adequately maintained on 100 mg. to 200 mg. per day.

SUPPLY: 50 mg. and 100 mg. tablets; bottles of 100, 1000 and 5000.

SQUIBB *Squibb Quality—the Priceless Ingredient*

"RAUDIXIN"® IS A SQUIBB TRADEMARK

DOXINATE®

A Better Answer to the Problem of Constipation

Permits normal bowel habits—"... [Doxinate] certainly seems to be a better answer to this problem [constipation] than do any of the therapeutic agents previously available."[1]

Effective—"In all patients, the administration of dioctyl sodium sulfosuccinate proved to be an effective fecal softener."[2]

Gradual action—"The softening effect of ... [Doxinate] on the stool was apparent on the average in 48 hours."[1]

Nontoxic—"dioctyl sodium sulfosuccinate has wide usefulness in ... constipation ... without the danger of toxicity or decreasing effectiveness ..."[3]

Doxinate acts **only** on the bowel **content.**

Doxinate increases the wetting ability of intestinal fluids as much as 25 times. The resulting homogenization of fecal material makes the stool soft and yet well-formed for easy evacuation.

Doxinate is completely free of irritant laxative or "bulk" effect—nor is flatulence or oily leakage ever a problem.

Doxinate does not cause bowel movement. Instead, it **permits** normal bowel habits.

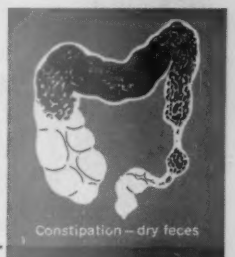
dosage:

Adults: one green 60 mg. capsule daily or one to three orange 20 mg. capsules daily.

Infants and children: 1 cc. or 2 cc. once daily in formula, milk or orange juice.

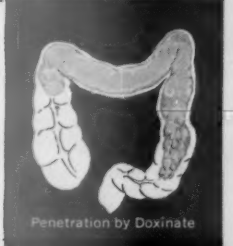
1. Spiesman, M. C., and Malow, L.: Journal-Lancet (June) 1956.
2. Antos, R. J.: Southwestern Med. *37*:236 (April) 1956.
3. Wilson, J. L., and Dickinson, D. G.: J.A.M.A. *158*:261 (May 28) 1955.

Permits normal bowel habits



Effective

Gradual action



Nontoxic

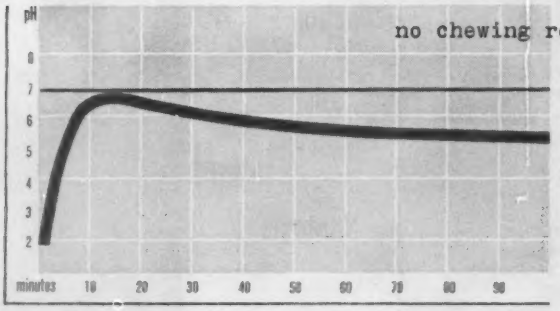
DOXINATE*

The original dioctyl sodium sulfosuccinate for constipation

LLOYD Brothers, Inc.
Cincinnati 3, Ohio
*Patent Pending

In the simple process of neutralizing stomach acid,

one antacid may work as well as another. Still, we think Syntrogel® 'Roche' is worth a trial because it's likely to work just a little bit faster (in a matter of seconds), last longer (often for hours), and the relatively small tablets "go down" so easily - no chewing required.



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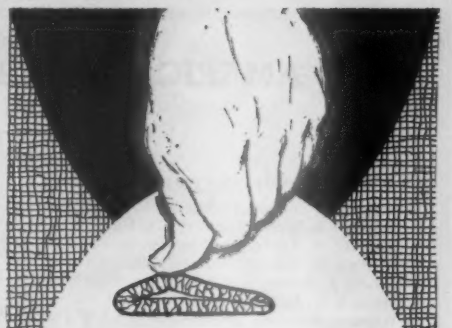

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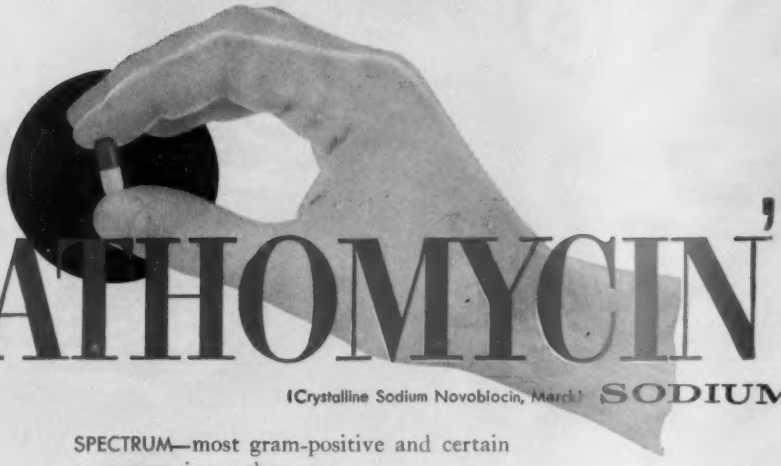

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1. Arnoff, B.: Personal communication. 2. Lazarte, J. A., and Petersen, M. C.: Personal communication.

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COLLEGES OF PHYSICIANS *

By G. F. STRONG, F.A.C.P., F.R.C.P.(London), F.R.C.P.(C), F.R.A.C.P.,
Vancouver, B.C., Canada

"PROFOUND, sad and discrete, groundedly learned, and deeply studied in physic" [1]—in these words, in the year 1518, the College of Physicians of London set out its requirements for members. The College was conceived by Thomas Linacre, the distinguished Englishman, whose education combined the trainings of humanist and physician. He took the degree of Doctor of Medicine at Padua with such a brilliant record, that on his return to England, he was promptly given a Doctorate in Medicine by both Oxford and Cambridge. Linacre remained at Oxford for a time, establishing a notable reputation as a Greek scholar, and translating into Latin some of the early Greek medical writings. About the turn of the century he moved to London where he became tutor and physician to the young Prince Arthur and later, personal physician to King Henry VIII. He was established as a leading physician and counted among his friends Thomas Wolsey the Archbishop of York, who was to become a cardinal not long before the founding of the College.

In those days, the practice of medicine in London was completely chaotic and uncontrolled, and any pretender or charlatan could flourish. In an attempt to improve this situation, an Act, passed in 1511, laid down that no person should practice physic or surgery within the City of London unless he had first been examined, approved, and licensed either by the Bishop of London, or the Dean of St. Paul's, acting with the advice of four doctors of physic or four expert surgeons. It is hard for us today to realize the power then exerted by the Church in secular and medical affairs, but there can be little doubt that when Thomas Linacre first planned his College of Physicians, he found it very helpful to be on terms of close friendship with the

* Presidential Address, Thirty-Seventh Annual Session, Los Angeles, California, April 18, 1956.

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Cardinal of England, the Bishop of London, and the Dean of St. Paul's. Their trust in his standards is indicated by the fact that, only seven years after the passing of the Act of 1511, the College of Physicians of London was:

> Incorporated and empowered, *independent of the hierarchy,* to forbid from practice of physic in London and within a precinct of seven miles around the City, any individual, graduates of Oxford and Cambridge excepted, who was not licensed by the President and the College.[1]

Four years later, these provisions were extended to the whole country.[1]

The College received a charter from King Henry VIII stating that it was established:

> to check men who professed physic rather from avarice than in good faith, to the damage of credulous people. Accordingly, after the example of other nations he had determined to found a College of the learned men who practiced physic in London in the hope that ignorant or rash practitioners might be restrained or punished.[2]

The English College was, therefore, endowed from the first with powers to examine and license, a fact that gave it both an academic and an administrative character. Over the years the College has assumed, in addition, many medico-political functions, all of which taken together give it an honored place among the English medical organizations. The aphorism that "every great institution is the lengthened shadow of a man" is certainly true in relation to Thomas Linacre and the Royal College of Physicians of London. He not only was responsible for bringing the College into being, but served as its first President for six years until his death in 1524.

Much of the credit for the enviable position which the College has achieved must be given to the wisdom of its founder. It might be profitable to consider further the three requirements from the members mentioned above. That a member must be "profound, sad and discrete" would seem to be a suitable means of securing conformity with professional standards of conduct. The use of the word "sad" must be taken as carrying its now obsolete meaning of fixed or established firmly, maturely steady, rather than its modern definition of affected by grief or downcast. Can anyone imagine a better description of a physician than that he should be profound, maturely steady, and discreet?

The second requirement—that members should be "groundedly learned" indicated the importance attached by Linacre to a broad basis of knowledge in the Natural sciences as a background for medical training. The purpose he had in mind is further revealed by the terms of the Linacre Lectureships, which provided for the exposition of those medical texts which to him were the basis of professional knowledge. The tremendous range of such knowledge today only emphasizes the appeal of the idea that the members of a College of Physicians should be "groundedly learned."

The last requirement, that they be "deeply studied in physic" set the high

standard of a College of Physicians in a phrase that well characterizes the professional competence of the members of that College.

In 1915, nearly four hundred years after the establishment of the English College, the inspiration derived from attendance at a meeting of the Royal College of Physicians of London resulted in the founding of this American College. But the circumstances of medical education, licensure, and practice were entirely different in the America of 1915 and the England of 1518. The original objects of this College were:

"(a) maintaining and advancing the highest possible standards in medical education, medical practice, and clinical research;
(b) perpetuating the history and best traditions of medicine and medical ethics,
(c) maintaining both the dignity and the efficiency of Internal Medicine in its relationship to public welfare."

Actually it was not until more than ten years after the founding of this College—and then due to the leadership and inspiration of two men, Dr. Alfred Stengel of Philadelphia, and Dr. Charles F. Martin of Montreal, that real progress began to be made toward the achievement of our present position in American Medicine.

This College, while called "American" has always included Canadian physicians among its members. In spite of the fact that a Royal College of Physicians and Surgeons was established in Canada in 1930, there has not been, nor should there be, any conflict between the two Colleges on this continent. Each fills a rôle that does not conflict with the other. The Canadian College has followed the English plan and conducts examinations for certification or Fellowship. The American College has delegated the duty of conducting examinations to the American Board of Internal Medicine, established by the joint efforts of this College and the section of Internal Medicine of the American Medical Association, and retains under its special jurisdiction, the maintenance of standards of professional competence.

Other notable Colleges of Physicians in the English-speaking world include the Royal College of Physicians of Edinburgh established in 1681 and the Royal College of Physicians of Ireland in 1667.

The newest College of Physicians in English-speaking countries is the Royal Australasian College of Physicians founded in 1938 and including members and Fellows in Australia and New Zealand. It was my honor and pleasure to go as your representative to those countries to attend their recent Annual Meeting held in Wellington, New Zealand, March 19 to 23. The meeting was an excellent one and the scientific program, including papers and clinical presentations, was of high order. For their tenth President, the Royal Australasian College elected Dr. E. G. Sayers of Auckland, the first New Zealander to occupy that post. In the course of this trip, it was my privilege to visit Sydney, Canberra, and Melbourne in Australia as well

as Christchurch, Wellington and Auckland in New Zealand. In both countries the standard of medical practice as shown in the teaching hospitals visited, was of the highest order. The examinations conducted by the Royal Australasian College are comparable to those of the Royal College of Physicians of London and the American Board of Internal Medicine.

This brief survey brings me to the theme of this address—the desirability of closer coöperation among the various English-speaking Colleges of Physicians. In view of the fact that Medicine is international and admits of no boundaries, coöperation among medical men in general and physicians in particular is obviously desirable. There is, in addition, the very apparent need for solidarity among the Western nations and particularly the English-speaking countries.

In these days of rapid advance in medical knowledge, there are many problems presented by the tempo of that advance. It has become virtually impossible for any medical man to keep abreast of all the newer concepts that are being introduced into Internal Medicine, and, as one result, we are finding more and more of the younger men becoming interested in a subspecialty or one phase or one part of the whole subject of Internal Medicine. Some of my predecessors in office have attempted to define an Internist, but with the rapid expansion of knowledge now necessary for a practitioner of Internal Medicine, the definition becomes more and more difficult. This expansion includes a greater familiarity with chemistry, as, for example, in the growth of hormone and steroid therapy, and with electronics, as in the medical use of radioactive isotopes. The abundance or superabundance of new medicaments and other preparations presented to the medical profession for use in diagnosis or treatment is overwhelming. Barr has recently pointed out that in 1953 fourteen thousand new substances were made available and these were added to a list of ten times that number already known to medicine.[3]

All this new knowledge, and this enormous number of new preparations present problems in medical education at every level, undergraduate, graduate, and postgraduate, and demand many adjustments in practice. Paralleling the tremendous advances in our knowledge is the increase in problems of delivering medical service to the public. All over the world, the idea of health insurance, voluntary or compulsory, is gaining greater acceptance. As part of a social security program, health insurance appeals to the public as a means of meeting the rising costs of medical care. But, as is well known, the increase in the cost of medical care is not a result of higher fees to doctors, but of the enormous increase in the *costs* of hospital services, of expensive diagnostic aids, of nursing care, and of all the other elements of a complete health program.

In view of the rapid advance in medical knowledge and of the impact of Health Insurance, both voluntary and compulsory, on the practice of medicine and particularly on the practice of Internal Medicine, it would seem

doubly important that all Colleges of Physicians should interchange ideas and the knowledge gained from experiences with these changes. The purposes of such a sharing of views and experience would be information and clarification. There are those who argue that this College should adopt a policy toward or take an active part in medical economics. But we should remember that a College is primarily academic. While serving as a means of raising the standards of practice, it should maintain that essential freedom which is inherent in the academic rôle. The College should display an active interest in the changing conditions of our times but it should have no part in actual decisions concerned with the economic aspects of medicine.

I am not denying that there is general dissatisfaction on the part of Internists with the fact that county, state, and national medical organizations, which are influenced largely by general practitioners and surgeons, display little interest in medical economics as related to Internists. As a result of this dissatisfaction, local, state or provincial societies for Internal Medicine are being organized to meet the need. It must be remembered that, while the great majority of our members are engaged in practice on a full-time basis, there are many who engage in part-time teaching, some who are in full-time teaching or in research, and others occupied with administrative posts. The interest in, and appreciation of, the importance of the economic aspects of Internal Medicine is not the same for all these groups. Since the economic side of medicine is handled almost entirely on a state or provincial basis, we should be satisfied to leave such matters to these newly organized state or provincial societies for Internal Medicine to which I have already referred. As the influence of the American College of Physicians increases, we should continue to expand our efforts to assist in graduate education through our Fellowship program, and on a broader hemispheral scale, through the more recent development of the Latin-American Fellowships. In addition, it is my personal hope that some way may be found to assist young men and women resident in Sterling areas who wish to come to this continent for graduate study. On the postgraduate level, we must endeavor to offer good annual and regional meetings and refresher courses. In line with the general idea of better Internist coöperation, the American College should continue to explore the possibility of a more active liaison and exchange of speakers with the other English-speaking Colleges. Just as our Universities are strengthened by additions to their faculties from other Universities, so each College could gain strength and knowledge from the others.

It is the pleasant duty of the President in concluding his address, to deliver a charge to the newly inducted Members. This duty takes on added significance when we realize that the members inducted tonight will provide the Governors, Regents, and Officers in another twenty to thirty years. It is my hope that those we welcome tonight will take seriously the Membership Pledge and will regard the College of Physicians as an organization

to be cherished with pride, to be kept free of those economic problems best handled by other societies, and to be recognized as the most effective institution for constantly raising the standards of the practice of Internal Medicine on this continent.

After four hundred and thirty-eight years, it is still appropriate that we should enjoin you new members to be:

> "Profound, sad and discrete; groundedly learned; and deeply studied in physic."

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TREATMENT OF CHRONIC CONGESTIVE HEART FAILURE WITH NEOHYDRIN FOR FROM EIGHT TO 65 MONTHS * †

By GEORGE C. GRIFFITH, M.D., F.A.C.P., SIM P. DIMITROFF, M.D., F.A.C.P., and M. C. THORNER, M.D., F.A.C.P.,
Los Angeles, California

THE most widely studied, recently introduced oral mercurial diuretic has been chlormerodrin (3-chloromercuri-2-methoxypropylurea), registered under the name of Neohydrin.† The indications for and limitations of oral organomercurial diuretics in the treatment of chronic congestive heart failure have been reported.[1]

Since Neohydrin is a relatively new medication, its effects after prolonged usage have received limited notice.[2] It is the purpose of this study to evaluate its degree of effectiveness during a period of time of from eight to 65 months. In addition, due to the widespread belief that the principal toxicity of organomercurial diuretics appears in the kidney, especial attention was directed to this organ for evidences of injury.

METHODS AND MATERIALS

Twenty-three patients with chronic congestive heart failure of duration varying from seven months to 18 years were studied. They were seen in the adult outpatient cardiac clinics of the Los Angeles County Hospital and also in private practice. The age variation was from 33 to 82. Arteriosclerotic heart disease was the most common entity, although a significant number had inactive rheumatic heart disease. Hypertension and cor pulmonale were also represented.

They were given Neohydrin tablets, each containing the equivalent of 10 mg. organic mercury. The duration of observation varied from eight to 65 months. The dose of drug was from one to three tablets daily, although at times there were changes from this schedule as necessitated by the clinical status of the patient. Tables 1 and 2 show further details of the dosage. Patients were first seen at weekly intervals, but when efficacy and tolerance to the drug were confirmed the observation interval was prolonged to one month or longer.

Criteria for the effectiveness of the drug consisted of maintenance of

* Received for publication January 30, 1956.

From the Department of Medicine (Cardiology), University of Southern California School of Medicine, and the Los Angeles County Hospital, Los Angeles, California.

Requests for reprints should be addressed to George C. Griffith, M.D., P. O. Box 25, 1200 North State St., Los Angeles 33, California.

† The Neohydrin was kindly supplied by the Lakeside Laboratories, Inc.

TABLE 1

Patients in Congestive Heart Failure with Albuminuria or High Nonprotein Nitrogen or Both, Treated with Neohydrin 9 to 65 Months

Name	Age	Diagnosis + Congestive Heart Failure	Initial Wt. Loss with Mercurial Parenteral Injections (Lbs.)	Daily Dose of Neohydrin Tablets	Albumin in Urine during Therapy	NPN at Beginning of Oral Therapy (Mg. %)	NPN after Indicated Interval Observation		NPN at End of Observation Period		Results and Comment
							(Mg. %)	(Mos.)	(Mg. %)	(Mos.)	
S. F. H.	60	A.S.H.D.	36	2–	+2–0	96	40	9	—	—	Good results for 9 months. Died from acute right ventricular failure
F. P.	81	A.S.H.D.	8	1–3	+1–trace	39	41	36	42	48	Very good results
J. C.	59	A.S.H.D.	6	1–2	0	36	36	31	32	43	Good results
A. W.	69	A.S.H.D.	11	2–	+1–trace	44	38	11	Not available		Good results clinically after 23 months
C. L.	65	A.S.H.D.	14	2–3	0	48	36	15	38	27	Good results
A. S. P.	67	Cor pulmonale	20	2–3	+1–trace	41	40	26	46	38	Good results
J. P.	65	A.S.H.D.	7	1–	+1	80	40	9	No follow-up		Good results up to 9 months
J. M.	69	A.S.H.D.	6	1–	+1	36	38	10	No follow-up		Good results up to 10 months
R. H.	82	A.S.H.D.	3	1–	+1–0	42	36	19	44	31	Good results
M. G.	37	R.F.H.D.	15	1–2	+2–trace	33	41	33	42	45	Good results
J. D.	80	H.T.H.D.	20	1–3	0	42	36	53	64	65	Good results for 4 years. In past year repeated bouts acute pulmonary edema. In terminal stages at present
H. A.	43	R.F.H.D.	0	2	+2–0	—	—	15½	36	27½	Good results

A.S.H.D.—Arteriosclerotic heart disease.
R.F.H.D.—Rheumatic fever heart disease.
H.T.H.D.—Hypertensive heart disease.

TABLE 2

Patients in Congestive Heart Failure without Renal Changes Treated with Neohydrin for from Eight to 17 Months

Name	Age	Diagnosis + Congestive Heart Disease	Frequency and Duration Mercuhydrin Injections (2 c.c.) Prior to Oral Therapy		Daily Dose of Neohydrin and Duration		Results	Albumin in Urine
			(Injections per Mo.)	(Mos.)	(Tablets)	(Mos.)		
L. B.	59	Rheumatic heart, aortic stenosis, and insufficiency	2 to 4	5	2	17	Good	0
M. E.	60	Hypertensive heart disease	None		1½	13	Good	0
J. S.	62	Chronic coronary disease, diabetes mellitis	2	24	1 to 2	15	Good	0
J. H.	44	Rheumatic heart, mitral stenosis	4	6	2	8	Good	0
C. R.	63	Chronic coronary disease	2	4	2 to 4	8	Good	0
M. W.	76	Cor pulmonale	2	1½	2	8	Good	0
M. Z.	53	Rheumatic heart, diabetes mellitus	None		3	3½	Good	0
D. P.	60	Chronic coronary disease	None		3	8	Good	0
B. P.	53	Hypertensive and chronic coronary disease	4	14	2 to 3	8	Good	Trace
M. S.	78	Rheumatic heart, mitral insufficiency	None		1 to 2	8	Good	0
J. C.	32	Rheumatic heart, mitral and aortic stenosis	4	4	1	8	Good	0

"dry weight," and maintained reduction or absence of râles, peripheral edema and hepatomegaly. The patient's subjective improvement was, of course, an important factor. In some instances the patient had been initially treated with a parenteral organomercurial diuretic. After edema loss he was maintained on the oral preparation. In other cases the patients had been maintained on parenteral diuretics, and the maintenance schedule was changed to the oral drug.

Because of the concept that one of the main toxic manifestations of organomercurial diuretics affects the kidney, attention was particularly directed toward this organ. In this series of patients, renal, gastrointestinal or other forms of toxicity were not encountered.

All patients were in Class III C to D (American Heart Association Classification). Other indicated medication, such as digitalis preparations, low sodium diet and, occasionally, aminophylline, was included in the therapeutic regimen along with Neohydrin.

RESULTS

The findings are divided into two groups: (1) Twelve patients had high nonprotein nitrogen or albuminuria, or both, at the onset of treatment.

After primary renal disease was ruled out they were observed for further renal changes following initiation of oral organomercurial diuretics (table 1). (2) Eleven patients showed no albuminuria or other evidences of intolerance after prolonged administration of the drug (table 2).

Table 1 is of interest because of the justified scruples a physician would have in treating a patient with an organomercurial preparation in the presence of high nonprotein nitrogen or albuminuria. None of the 12 patients had primary renal disease. It was therefore concluded that the evidence of renal irritation was secondary to congestive heart failure, and that improvement of the latter should also improve the renal picture.

The reduction of high nonprotein nitrogen levels to normal or near-normal figures, after therapy of congestive failure (including daily Neohydrin) for periods of time of from eight to 65 months, strongly indicates that in these instances the nitrogen retention was due to the circulatory changes in the kidney resulting from heart failure. During this period of therapy small amounts of albumin continued to appear in the urine, as it did prior to Neohydrin therapy.

The following case histories are illustrative of the above observations:

Case Reports

Case 1. A 60 year old male had chronic cor pulmonale, diabetes mellitus and arteriosclerotic heart disease. When first seen he was markedly orthopneic and cyanotic and extremely ill. Vital capacity was 24% of normal. Nonprotein nitrogen was 75.7 mg.%. One week later it was 96 mg.%, with 2-plus albuminuria.

He was digitalized and placed on a low sodium diet. After the absence of primary renal disease had been ascertained he was given parenteral organomercurials for two weeks. He lost 36 pounds in weight. He was then maintained on two tablets of Neohydrin daily. The nonprotein nitrogen fell to 40 mg.% and the urine was free of albumin. He was able to stay free of edema for nine months on this dosage, without any evidence of renal or other toxicity. He died suddenly from acute right heart failure.

Comment: The elevated nonprotein nitrogen and albuminuria were a manifestation of severe congestive failure. Amelioration of the latter and maintenance of its improvement with Neohydrin for nine months corrected the renal abnormality. It is obvious that withholding the diuretic in this instance for fear of further renal aggravation would have done more harm than good.

Case 2. A 75 year old male had hypertensive and arteriosclerotic heart disease. He was placed on a low sodium diet and digitalized with gitalin. There was no clinical evidence of kidney pathology. The indications for diuretic therapy were clearly seen when he lost 20 pounds of weight following parenteral organomercurials at the onset of therapy.

In January, 1951, he was started on Neohydrin, one tablet daily. The dosage has varied from one to three tablets since that time, a period of more than 65 months. Nonprotein nitrogen at the beginning of therapy was 42 mg.%, and at the end of 65

months was 64 mg.%. Repeat urinalyses have failed to demonstrate albuminuria. There was no evidence of intolerance in other organ systems. He has had repeated attacks of severe acute pulmonary edema.

Comment: The 65 month period during which this patient was using one to three tablets of Neohydrin daily is the longest time of observation in this series. The contribution of Neohydrin to the control of congestive failure during the period of more than five years is self-evident.

Case 3. An 81 year old male had arteriosclerotic heart disease with right bundle branch block and paroxysmal auricular tachycardia. He was digitalized and given organomercurial diuretic injections, after which he lost eight pounds and felt remarkably improved. He took one Neohydrin tablet daily, after his biggest meal, for 36 months. His nonprotein nitrogen prior to therapy was 39 mg.%, and after 36 months it was 41 mg.%. It was 42 mg.% after 48 months. The original 1 plus albuminuria decreased to a trace after 48 months.

Comment: Even nearing his ninth decade of life, this patient tolerated satisfactorily daily Neohydrin for four years. Another patient, age 81, as noted in table 1, tolerated a similar dose for 19 months without adverse effects. Indeed, eight patients in this subgroup were above age 60 and were able to use the drug to good advantage.

Table 2 consists of the second group of patients observed for from eight to 17 months. There was no albuminuria. There was no gastrointestinal intolerance in this group. The dosage here varied from one to four tablets daily. Here, too, one-half of the patients were age 60 or more.

Discussion

Neohydrin has been described as one of the most efficient organomercurial diuretics available.[3, 4] The present study has confirmed its efficacy in a series of patients treated with it daily for periods of time as long as five years.

Injury to the epithelium of the renal tubules from continued use of organomercurial diuretics has long been considered one of the dangers of this drug. In this series there was no clinical evidence of such damage attributable to the drug.

Histologic study of the kidneys was possible in one patient (case 1) who initially had severe congestive heart failure with albuminuria and high nonprotein nitrogen. He had been on Neohydrin, two tablets daily for nine months. The congestive symptoms were controlled and the renal abnormalities disappeared. He suddenly died of acute right heart failure. Postmortem examination showed normal kidneys except for passive congestion. There was no tubular damage.

Albuminuria is not a rare occurrence in congestive heart failure. Scheifley and associates [5] studied 161 cases of congestive heart failure at autopsy. Eighty-eight per cent had previous evidence of albuminuria.

However, histologic study of the kidneys in these patients revealed normal structure, or minor lesions thought not responsible for the proteinuria. They found a good correlation between the grade of albuminuria and the degree of congestive failure. They even commented that Grade 4 albuminuria could exist in patients with congestive heart failure who had histologically normal kidneys.

Findings in the present study indicate that albuminuria and high nonprotein nitrogen are not necessarily a contraindication to this oral organomercurial diuretic. Kaplan and associates [6] arrived at similar conclusions. Improvement in the renal findings often occurred with improvement of the congestive failure following therapy.

Neohydrin, however, is definitely contraindicated in the presence of primary renal disease. Active digestive tract disease and allergy are the other contraindications.

It is of interest that the older age groups were able to tolerate this drug for periods of up to five years without evidence of untoward effects. More than half of the patients studied were more than 60 years of age.

Conclusions

1. Twenty-three patients, more than half of whom were over age 60, who were in chronic congestive heart failure, were treated with Neohydrin for a period of time varying from eight to 65 months, with satisfactory results.

2. Patients without primary renal disease, but with albuminuria and high nonprotein nitrogen due to congestive circulatory changes, can be adequately and safely treated with Neohydrin for long periods of time.

Summario in Interlingua

Neohydrina, un oral diuretico mercurial organic, esseva usate con resultatos satisfactori in le tractamento de congestive disfallimento cardiac debite a varie causas. Le dosages esseva adjustate a inter un e duo tablettas per die. In un regime con digitalis, dieta a basse contento de natrium, e altere indicate mesuras therapeutic, Neohydrina se monstrava efficace in le mantenentia non-edematose del patientes durante periodos de inter octo e 65 menses.

Patientes in disfallimento congestive con albuminuria e elevate nivellos de nitrogeno nonproteinic sed sin primari morbo renal manifestava un melioration de ille anormalitates durante lor curso de Neohydrina.

Al tempore presente le facto es recognoscite que sever grados de albuminuria pote occurrer durante le curso de congestive disfallimento cardiac. Elevate nivellos de nitrogeno nonproteinic pote accompaniar iste anormalitate. Le uso de Neohydrina, insimul con altere establite mesuras therapeutic pro le controlo de disfallimento cardiac, meliora le secundari dysfunction renal durante que le patiente es mantenite libere de edema.

Tamen, primari morbo renal remane un indication contra le uso de iste droga.

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THE EFFECTIVENESS OF AN ORAL VITAMIN K_1 IN CONTROLLING EXCESSIVE HYPOPROTHROMBINEMIA DURING ANTICOAGULANT THERAPY *

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Anticoagulant therapy with the coumarin and indandione derivatives has been made less hazardous by the demonstration that Vitamin K_1 and Vitamin K_1 oxide [1-5] produce a prompt reversal of excessive hypoprothrombinemia. Intravenous Vitamin K_1 in dosage varying from 50 to 500 mg. of the oil-soluble emulsion will effect the prompt return of an elevated prothrombin time approximately to normal within 12 hours in most patients, frequently accompanied by cessation of bleeding when a hemorrhagic complication is present.

The emulsion of Vitamin K_1, originally prepared for intravenous administration, has been reported also to be effective by mouth.[6-9] Hanson [7] found that the prothrombin time was reduced to normal or near normal levels within 24 hours by doses ranging from 500 mg. to as low as 50 mg. of the Vitamin K_1 emulsion given orally. Duff [8] observed that oral doses as small as 5 or 10 mg. restored the prothrombin time to a safe level as effectively as much larger oral doses. Wright [9] successfully employed dosages of Vitamin K_1 varying from 10 to 50 mg. to reduce an excessively prolonged prothrombin time to a safer level, and advised against amounts greater than 50 mg.

For effective anticoagulant therapy with the coumarin or indandione drugs, it is essential that the drug be used in sufficient amount so that the prothrombin time will be prolonged into the therapeutic range, thus bringing about the desired antithrombotic alteration of the coagulation mechanism. The therapeutic range is that spread of elevated prothrombin time wherein an antithrombosing effect is produced, but with as little risk as possible of inducing hemorrhagic complications, i.e., "safe but adequate" anticoagulation. In this laboratory the therapeutic range for treatment of a patient with an acute thrombo-embolic problem is considered to be between 22 and 35 seconds (normal, 15 seconds). The experience of the past decade has demonstrated that no further beneficial antithrombosing influence accrues when the prothrombin time rises above the upper limit of 35 seconds. Moreover a majority of the hemorrhagic complications encountered in this clinic [10]

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have occurred in association with prothrombin time values above this level. It therefore would appear reasonable and physiologic to return a prothrombin time elevated above 35 seconds to the safe therapeutic range as soon as possible, even though no bleeding has occurred. Furthermore, the impression has been gained that the fewer the days of excessive hypoprothrombinemia during a patient's treatment, the smaller the possibility of encountering hemorrhagic complications. In accordance with this philosophy of therapy, it has been customary in this clinic to employ promptly small doses of water-soluble Vitamin K parenterally, or Vitamin K_1 orally, whenever the prothrombin time test rises above 35 seconds in order to "damp down" this unnecessary hypoprothrombinemia and thus restore the prothrombin time as soon as possible to the "safe but adequate" therapeutic range.

During the last year a tablet of Vitamin K_1 has become available for oral use. Its ease of administration is an obvious advantage. The effectiveness of small doses of this form of Vitamin K_1 in the "damping down" therapy for excessive hypoprothrombinemia has been established. It is the purpose of this report to present these experiences with the oral tablet of Vitamin K_1 as an effective antidote for coumarin- or indandione-induced excessive prothrombinopenia.

Methods

1. *Patients:* A total of 75 patients on the ward or private services of the Presbyterian Hospital were studied. These individuals were receiving anticoagulant therapy with Dicumarol or Sodium Warfarin because of acute thrombo-embolic processes, principally cardiac infarction, thrombophlebitis or pulmonary embolism. In two instances the anticoagulants were being administered prophylactically.

2. *Prothrombin Time:* The prothrombin time tests were determined by the Link-Shapiro modification of the Quick technic.[11] The normal control value was 15 ($\pm$ 1) seconds.

3. *Vitamin K_1:* A tablet of 5 mg., which could easily be halved to 2.5 mg. when desired, was made available by Merck & Co. The dosages of Vitamin K_1 which were employed ranged from 2.5 to 20 mg.

4. *Outline of Study:* When the prothrombin time of a patient under anticoagulant therapy was determined as above 35 seconds, Vitamin K_1 was given in tablet form. The prothrombin time was determined approximately 12 hours after the medication. In six patients more frequent determinations of the prothrombin time were done.

Results

Fifteen patients with prothrombin values ranging between 35 and 49 seconds received 2.5 mg. of Vitamin K_1 orally (table 1). Eleven of the 15 (73%) returned their prothrombin time from above the upper level of

the therapeutic range to a safe value (35 seconds or less) within 12 hours. Four of the five not responding at 12 hours were within the safe therapeutic range when tested 24 hours after the Vitamin K_1. Two of the 15 showed a reduction below the lower limit of the therapeutic range (22 seconds), and in these two patients heparin was administered as a supplementary anticoagulant to ensure a continuing antithrombotic effect until the prothrombin time became satisfactorily elevated again by additional doses of the prothrombinopenic anticoagulant agent.

Thirty-one patients whose prothrombin values ranged from 36 to 59 seconds were given 5 mg. of Vitamin K_1 orally (table 2). Twenty-eight of the 31 individuals (90%) had returned their prothrombin times from the excessive values to 35 seconds or less within 12 hours. The three patients who had not responded by returning to a safe range of prothrombin

TABLE 1

The Effect of Oral Administration of 2.5 mg. Tablet Vitamin K_1 on the Prothrombin Times of 15 Patients with Coumarin-Induced Hypoprothrombinemia

	Prothrombin Time (seconds)	
Patient	Before Vitamin K_1	12 Hrs. after Vitamin K_1
1	35	21
2	40	25
3	38	29
4	46	30
5	46	39
6	42	23
7	38	22
8	44	45
9	45	50
10	38	38
11	39	25
12	40	21
13	49	25
14	44	27
15	48	24

time elevation at 12 hours had responded satisfactorily when tested 24 hours following Vitamin K_1. Six of the 31 showed a reduction below the lower therapeutic range (22 seconds) and were consequently given supplementary heparin.

Eighteen patients with prothrombin values ranging between 38 and 75 seconds received 10 mg. of Vitamin K_1 orally (table 3). Seventeen of the 18 (94%) had returned their prothrombin times to a safe range (35 seconds or less) within 12 hours. One patient failed to respond satisfactorily at both 12 hours and 24 hours. Three of the 18 returned their prothrombin to below the therapeutic range and received supplementary heparin to ensure continuing effective anticoagulation.

Ten patients with prothrombin values between 32 and 65 seconds were given 15 mg. of Vitamin K_1 tablets orally (table 4). Seven of the 10

TABLE 2

The Effect of Oral Administration of 5 mg. Tablet Vitamin K_1 on the Prothrombin Times of 31 Patients with Coumarin-Induced Prothrombinopenia

Patient	Prothrombin Time (seconds)	
	Before Vitamin K_1	12 Hrs. after Vitamin K_1
1	43	24
2	38	32
3	41	20
4	37	25
5	45	24
6	47	26
7	42	27
8	39	27
9	45	35
10	40	47
11	39	20
12	40	22
13	45	21
14	45	21
15	46	21
16	59	53
17	45	34
18	58	29
19	36	22
20	38	22
21	39	33
22	46	25
23	43	28
24	47	43
25	42	20
26	46	32
27	45	39
28	46	25
29	38	24
30	36	31
31	42	26

TABLE 3

The Effect of Oral Administration of 10 mg. Vitamin K_1 (Tablet) on the Prothrombin Time of 18 Patients with Coumarin-Induced Prothrombinopenia

Patient	Prothrombin Time (seconds)	
	Before Vitamin K_1	12 Hrs. after Vitamin K_1
1	45	24
2	38	23
3	50	24
4	40	27
5	56	31
6	64	30
7	75	19
8	44	26
9	42	32
10	46	28
11	53	55
12	45	20
13	65	17
14	47	24
15	47	26
16	50	31
17	43	18
18	40	25

TABLE 4

The Effect of Oral Administration of 15 mg. Vitamin K_1 (Tablets) on the Prothrombin Time of 10 Patients with Coumarin-Induced Prothrombinopenia

Patient	Prothrombin Time (seconds)	
	Before Vitamin K_1	12 Hrs. after Vitamin K_1
1	65	42
2	57	15
3	40	47
4	32	18
5	56	32
6	55	31
7	55	35
8	37	30
9	49	45
10	57	22

(70%) returned to a safe level within 12 hours. The three who failed at 12 hours had returned to safe levels of prothrombin time at 24 hours. Two of the 10 showed a prothrombin time below the minimal therapeutic range at 12 hours and needed temporary heparin supplementation until the re-establishment of adequate prothrombin deficiency.

One patient with a prothrombin time of 71 seconds was given 20 mg. of Vitamin K_1 tablets orally and reverted to 21 seconds in 12 hours. He also received temporary heparin therapy.

Six patients were studied at more frequent intervals to determine more precisely the duration of the latent period following oral Vitamin K_1 before the return to the therapeutic range was effected (table 5). Four patients with prothrombin time values between 36 and 58 seconds were given 5 mg. of Vitamin K_1 tablets orally, and two patients with prothrombin time values of 42 and 44 seconds were given 10 mg. The desired effect on the prothrombin time was demonstrable in two patients within four to six hours. By 10 to 12 hours the prothrombin time of each of the six individuals had returned to the safe range.

TABLE 5

The Effect of Oral Administration of Vitamin K_1 (Tablets) on the Prothrombin Time of Six Patients with Coumarin-Induced Prothrombinopenia

Patient	Dose of Vitamin K_1 (mg.)	Prothrombin Time (seconds)						
		Before Vitamin K_1	After Vitamin K_1 (hours)					
			2	4	6	8	10	12
1	5	58		38				29
2	5	36		24		24	25	
3	5	38	39	36	31	24	22	
4	5	39	42	37	44	37	33	
5	10	44		49	40	33	26	
6	10	42		43			32	

Discussion

The availability of a tablet form of Vitamin K_1 for oral use provides a drug which is both effective and easily administered, and offers, together with the intravenous preparation, an added safeguard in prothrombinopenic anticoagulant therapy with the coumarin and indandione derivatives.

This form and routine of administration of Vitamin K_1 is effective in restoring an excessively elevated prothrombin time to the safe therapeutic range (below 35 seconds) within 12 hours in approximately 85% of patients in this study, and in practically all patients (98%) within 24 hours.

It is apparent that some individuals in this study would have returned their prothrombin times to the safe range within 12 to 24 hours even without the assistance of Vitamin K_1. However, the experience with Dicumarol and Sodium Warfarin in this clinic is that a majority of patients remain above the upper limit of safe therapeutic range for 24 to 96 hours or even

Table 6

The Rate of Spontaneous Return of Excessively Elevated Prothrombin Time Value to the Therapeutic Range in 232 Patients Treated with Dicumarol

Number of Patients	Initial Prothrombin Time Value (seconds)	Number of Patients Whose Prothrombin Time Returned to Therapeutic Range Within:				
		24 Hrs.	48 Hrs.	72 Hrs.	96 Hrs.	120+ Hrs.
64	35–39	37(58%)	15(23%)	10(16%)	2(3%)	
134	40–49	35(26%)	56(42%)	28(20%)	8(6%)	7(5%)
22	50–59	4(18%)	8(36%)	8(36%)	2(9%)	
9	60–69	1(11%)	2(22%)	3(33%)	2(22%)	1(11%)
2	70–79			1	1	
1	80 89				1	
232		77(33%)	81(35%)	50(21%)	16(7%)	8(4%)

longer, provided Vitamin K or Vitamin K_1 is not being used to hasten the reversion. In 232 patients treated with Dicumarol in whom the prothrombin time rose above the therapeutic range (table 6), only 33% had returned spontaneously to the safe level below 35 seconds in 24 hours, another 34% at 48 hours, and an additional 21% by 72 hours. Twelve per cent remained above the upper limits of the safe therapeutic range for 96 hours or longer. The rate of return is slower in direct relation to the height of the prothrombin time, e.g., 57% of the patients in the 35–39 second range had returned to safe values at 24 hours, while only 18% of the 50–59 second group had accomplished this spontaneous return at a comparable period. Moreover, a small group of patients are encountered in whom the prothrombin time rises to high levels and may be maintained in this dangerous zone for periods as long as seven to 12 days before spontaneously returning within the therapeutic range. In some of this latter group a complicating hemorrhage

may occur after several days of consistent maintenance of the unnecessarily elevated prothrombin value.

The dosage plans of 2.5 mg. and 15 mg. seemed somewhat less successful than those employing 5 mg. and 10 mg., but was not appreciably different at the 24 hour period. Moreover, the differences noted do not appear to be statistically significant. The selection of the appropriate oral dosage of Vitamin K_1 tablets depends on a consideration and evaluation of several factors, including the height of the prothrombin time, the rate at which the prothrombin time is becoming prolonged, the state of Vitamin K stores in the body as judged by factors of general health, liver status, state of nutrition and recent use of oral antibiotics, the amount of and immediacy with which the oral coumarin or indandione compounds have been administered, i.e., the larger the dosage of the prothrombinopenic drug and the more recent its ingestion, the greater the need for a larger amount of Vitamin K_1.

The 2.5 to 15 mg. doses of oral Vitamin K_1 have the advantage of avoiding the production of a state of resistance to continuing prothrombinopenic anticoagulant therapy with subsequent doses of the coumarin or indandione drugs, such as the increased requirement for Dicumarol which had been encountered after the intravenous injection of the larger doses of 500 to 1,000 mg. of the Vitamin K_1 emulsion.

The use of the smallest effective amount of Vitamin K_1 is desirable. A disadvantage of employing oral Vitamin K_1 is that, despite the small dosage, the prothrombin time dropped below the lower level of the therapeutic range (22 seconds) to a value inadequate for an antithrombotic effect in an appreciable number (approximately 15%) at 12 hours. A similar result is to be expected in an additional small number at 24 hours or 36 hours following Vitamin K_1 ingestion. However, since it is possible to maintain a continuing antithrombotic effect by the prompt institution of heparin as an interim supplementary anticoagulant, this does not pose the serious problem of allowing a lapse in effective anticoagulation. It does, however, emphasize the necessity of careful supervision of the prothrombin time reports and estimation of the subsequent days' anticoagulant doses. The prompt administration and the occasional use of a larger amount of the oral prothrombinopenic agent 18 hours after the Vitamin K_1 will assist in maintaining or reestablishing adequate elevation of the prothrombin time.

Oral use of Vitamin K_1 is less effective than the parenteral administration, and entails an appreciably higher dosage than when given intravenously. Rehbein and his associates,[3] employing the Vitamin K_1 emulsion intravenously in dosage as low as 0.5 mg. to 2.5 mg., were able to reduce excessively elevated prothrombin values in a manner similar to the one described in this study. This would appear to establish a dosage ratio of the order of approximate magnitude of 5 : 1 between the oral and intravenous routes.

The advantage of an oral tablet form of Vitamin K_1 provides another

safeguard for out-patient ambulatory anticoagulant therapy. It now becomes possible for each patient in an ambulatory treatment program to have his own personal supply of Vitamin K_1 tablets, thus removing the practical obstacle of a physician being necessary for the intravenous injection of the Vitamin K_1 emulsion. In both hospitalized and ambulatory patients, the use of Vitamin K_1 tablets by mouth appears to constitute an appreciable augmentation to the safety and practicability of anticoagulant therapy.

Summary

1. A Vitamin K_1 tablet for oral administration has become available. This drug, in doses of 2.5 mg. to 20 mg., was administered to 75 patients in whom excessively elevated prothrombin time values were produced by prothrombinopenic anticoagulant therapy.

2. In 85% of the patients studied the prothrombin time returned to a safe range (35 seconds or less) within 12 hours after the oral administration of Vitamin K_1 in this dosage, and in 98% of the patients within 24 hours.

3. The prothrombin time fell below the lower therapeutic level of adequate anticoagulation in 15% of the patients at 12 hours following Vitamin K_1. Under such circumstances the administration of heparin ensured a continuing antithrombotic effect, until subsequent doses of coumarin or indandione agent again achieved an adequate hypoprothrombinemia.

4. Since most hemorrhages during anticoagulation occur in association with prothrombin time values above 35 seconds, Vitamin K_1 tablets for oral use provide an additional safeguard in coumarin and indandione therapy.

Summario in Interlingua

Circa 85% del serie hemorrhagias que occurre in le curso de hypoprothrombinemic therapia anticoagulante es associate con augmentos del tempore prothrombinic a plus que 35 secundas. Per consequente il pare logic e physiologicamente desirabile reducer un excessivemente elevate tempore prothrombinic le plus promptemente possibile a intra le limites therapeutic non-riscose, i.e. a infra 35 secundas, mesmo si nulle sanguination ha occurrite. Il es nostre impression que quanto plus restringite le numero del dies de excessive hypoprothrombinemia durante le tractamento de un patiente, tanto plus improbabile es le occurrentia de complicationes hemorrhagic.

Un tabletta de Vitamina K_1 pro administrationes oral ha devenite disponibile. Iste droga, in doses de inter 2,5 e 20 mg, esseva administrate a 75 patientes in qui excessive augmentos del tempore prothrombinic habeva resultate del prothrombinopenic therapia anticoagulante.

In 85% del patientes studiate le tempore prothrombinic retornava a intra le limites therapeutic non-riscose (i.e. a infra 35 secundas) intra 12 horas post le administration de Vitamina K_1. In 98% del patientes le mesme effecto se produceva intra 24 horas.

Le tempore prothrombinic recedeva a infra le nivello therapeutic inferior de adequate anticoagulation in 15% del patientes post 12 horas post le administration de Vitamina K_1. Isto non es un serie disavantage. Sub tal conditiones le administra-

tion de heparina assecurava un continue effecto antithrombotic usque doses additional de cumarina o de indandiona restaurava de novo un adequate hypoprothrombinemia.

Proque le majoritate del hemorrhagias durante therapias anticoagulante occurre in le presentia de tempores prothrombinic de plus que 35 secundas, oral tablettas de Vitamina K_1 representa un facilemente administrate protection additional in therapias prothrombinopenic a cumarina e indandiona.

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SECONDARY AMYLOIDOSIS IN LEPROSY *

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IN the National Leprosarium of the United States the leading cause of death in leprosy is secondary amyloidosis. The amyloidosis has been associated only with lepromatous disease, but has not been limited to cases of advanced disease or to cases showing extensive ulcerative processes. It may be seen in relatively young people who have had active lepromatous leprosy for only a few years or who have had leprosy of longer duration, but show minimal changes except for positive skin scrapings for *Mycobacterium leprae*. Amyloidosis may also occur in cases of longer duration which have been aggravated by chronic secondary infections, or in which recurrent erythema nodosum leprosum has been prominent.[1]

The primary objective of this study was to find a method of diagnosing amyloidosis at an earlier stage than is possible with the Congo red test. The first approach was to correlate Congo red findings with clinical and autopsy material. The next step was the study of serum protein patterns in known cases of amyloidosis parallel with controls in an effort to find a consistent pattern which might be of assistance in determining which cases have or will develop amyloidosis, and also to study the effect of large doses of hyaluronidase on the serum protein pattern, proteinuria and hepatosplenomegaly in amyloidosis. A third, very limited study was to obtain liver biopsies with the Vim-Silverman needle in cases of known amyloidosis (as evidenced by the Congo red test), and in cases in which amyloidosis was not apparent.

Usually the first sign of this complication is the development of persistent proteinuria which becomes progressively more severe. Renal involvement has occurred in 100% of our cases of proved secondary amyloidosis. The liver, spleen, lymph nodes, pituitary and adrenal glands, and gastrointestinal tract are also frequently involved.

A BRIEF CLASSIFICATION AND PATHOLOGY OF AMYLOIDOSIS

Amyloidosis presents no constant pathologic or clinical picture. It is classified into primary, secondary, that associated with multiple myeloma, and localized forms. Secondary amyloidosis occurs in a variety of diseases, especially those of long standing.[2]

The nature of amyloid is largely limited to the pathologist's description

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based on staining affinities and general characteristics noted in routine hematoxylin and eosin sections.[3, 4] The chemical composition is unknown; however, the work of Hass et al.[5] supports the belief that it is a fundamental protein unit plus a sulfate-bearing polysaccharide, and that it varies in chemical composition, comprising a group of closely related substances. The pathogenesis and etiology are poorly understood, although the fundamental feature is the intracellular deposition of the amyloid material.[6, 7]

The various etiologic theories of amyloid disease are based upon disturbances in protein metabolism. This is supported by the protein composition of amyloid, and also the development of amyloid in animals who are fed sodium caseinate.[8] Others [9, 10] hold that it is an antigen-antibody reaction, the theory of which is based upon the frequent association of chronic inflammatory diseases which result in prolonged stimulation of immune mechanism, and also on the incidence of amyloidosis in horses which are used for the production of high titered antisera.[11] It is also postulated that amyloidosis is related to a disturbance of the reticuloendothelial system,[12] which is supported by the fact that amyloid frequently involves structures that are related to this system. Finally, it is thought that amyloid is related to a hyperglobulinemia,[13, 14] because of the incidence of amyloidosis in multiple myeloma and other diseases which tend to have an elevated serum globulin fraction. Recent experimental work of Richter [15] tends to clarify some of the above hypotheses. He was able to produce amyloidosis in rabbits by the repeated injection of ribonucleotide, which is known to produce serum globulin in animals. The amyloidosis produced was associated with an increase of the serum beta globulin and the $alpha_2$ globulin, the gamma fraction remaining essentially normal in this experiment. In the study of fibrinoid by Altshuler and Angevine [16] the formation of metachromatic material was closely related to the processes of hyalinization, amyloid formation and tissue sclerosis; in this fibrinoid change the precipitation of acid polysaccharide of the ground substance had occurred. Graham [17] noted a close relationship between amyloid degeneration and other disease processes which alter the chemical nature of ground substances and connective tissue. Jackson and Slavin [18] observed that experimental hyperglobulinemia is related to amyloidosis, and that hyperglobulinemia is a response to injury of connective tissue. These same authors have recommended the use of ACTH and cortisone because of their effect on ground substances.

Recent experimental work by Latvalahti [19] and Teilum,[20] however, has shown that ACTH and cortisone administration in animals can produce amyloid. Such an effect has not been observed in lepromatous leprosy complicated by erythema nodosum leprosum and treated for periods as long as eight months with cortisone and ACTH [21] in an effort to control the reaction. These patients have not developed clinical amyloidosis, although patients with this type of leprosy are very prone to develop amyloid disease during the natural course of their disease.

It is our feeling that amyloid is a protein polysaccharide complex which tends to vary in composition, that it is related to hyperglobulinemia or some specific fraction of the serum globulins, and perhaps in some way related to altered connective tissue structure and disturbed antibody-antigen relationship.

Methods and Material

The Congo red test was performed on 95 leprosy patients in various stages of the disease. Of the 95 cases, eight were of the tuberculoid type and 87 of the lepromatous. This test was repeated at intervals of one year in 24 of the cases, two years in 15 cases, and three years in one case.

The Congo red was given intravenously in a 1% aqueous solution in dosages of 1 c.c. of the solution per 10 pounds of body weight. Blood specimens were collected at the end of two minutes and one hour after the injection, the two minute specimen being used as the control. Urine specimens were examined for Congo red one hour after the administration of the dye. Normally the dye is ultimately excreted in the urine, but in only one case was this extensive enough to give a false-positive test, and that patient had marked proteinuria which undoubtedly bound the Congo red and permitted excessive dye loss within one hour.

Laboratory studies consisted of blood nonprotein nitrogen, total serum proteins, serum albumin, globulin, alpha, beta and gamma globulins, serum cholesterol, phospholipids, polysaccharides, mucoproteins, and liver function tests of thymol turbidity and cephalin-cholesterol flocculation. Urinalysis consisted of specific gravity, quantitative albumin, sugar, and microscopic examination. Serum polysaccharides were determined by the tryptophan reaction and expressed as Coleman units.[22] Mucoproteins were determined by the method of Winzler et al.[23] Methods for all other analysis have been previously reported from this laboratory.[24, 25, 26]

Table 1 indicates the parallelism, in 95 cases of leprosy, between the clinical evidences of amyloidosis and the data as to the Congo red test, the serum proteins, albuminuria, non-protein nitrogen, and the presence of hepatosplenomegaly. Twenty of these cases have since died, and 18 of the 20 were autopsied. Ten of the autopsied patients revealed amyloidosis of greater or less degree. Information relative to the 20 deaths is found in table 2 and discussed under that section.

Serum protein levels were 5.5 gm. per 100 c.c. or below in 28 of the 95 cases, and these showed a reversal of the albumin-globulin ratio. Of the 67 cases with normal serum proteins, moderate to marked hyperglobulinemia with reversal of the albumin-globulin ratio was noted in 22. These findings occur frequently in leprosy uncomplicated by amyloidosis. The highest blood nonprotein nitrogen was 110 mg.%. In 37 of the 95 patients, hyaline or granular casts, or both, were present in the urine, though the numbers were not excessive. The protein in the urine varied from a slight

amount to a large quantity. In instances where slight amounts of albumin were obtained there were days when no albumin was found upon qualitative examination. These cases, 10 in number, are not reported in the table as presenting proteinuria.

The diagnosis of secondary amyloidosis at Carville depends largely upon the following findings: persistent proteinuria; a Congo red absorption of at least 60% in one hour, and preferably 80%; hepatosplenomegaly and hyperglobulinemia, with or without hypoalbuminemia, and with no consistent alterations in the globulin fractions. Of these four points, the proteinuria has been a consistent finding with rare exception (case 16), and in our experience must be present to make the clinical diagnosis of secondary amyloidosis. A Congo red absorption of 80 to 100% likewise will establish the diagnosis, and proteinuria has always been found when the Congo red test has reached this level of absorption in this series. With decreasing

TABLE 1

Clinical Analysis and Congo Red Tests Parallel With Serum Proteins, Blood Nonprotein Nitrogen and Urinalysis on 95 Cases of Leprosy

Congo Red, Per Cent Absorption	Cases*	Cases with Albuminuria	Cases with Hyperglobulinemia	Cases with N.P.N. over 45 mg.%	Cases with N.P.N. from 40–45 mg.%	Cases with Enlargement of Liver and Spleen	Clinical Evidence of Amyloidosis	
							Good	Poor
0–20	7	1	0	3	4	0	0	1
20–40	31	6	11	13	6	6	2	6
40–60	24	8	12	13	5	7	6	2
60–80	14	4	7	13	2	4	4	2
80–100	19	18	19	15	2	18	19	0
Total	95	37	49	57	19	35	31	11

* Cases represent total numbers.

amounts of Congo red absorption in one hour, without the other changes mentioned, and particularly the proteinuria, the diagnosis of secondary amyloidosis becomes uncertain. A more clear cut picture is necessary before the clinical diagnosis can be definitely established. Some of the group with 60 to 80 Congo red absorption had diabetes mellitus, essential hypertension, nephrosclerosis or chronic pyelonephritis, which further confuses the clinical picture and makes the diagnosis even more uncertain. In the group with 40 to 60% Congo red absorption a clinical diagnosis of amyloidosis was made in six patients because they met the above criteria, except for the Congo red, and amyloidosis was considered highly probable in an additional two cases in this group.

With due consideration for the limitations of judging hepatosplenic enlargement clinically, hepatosplenomegaly is nearly always present in the advanced cases, but in the borderline group it is absent more often than present, so that clinically it has not been too helpful. Likewise, some of

these cases were found to have cirrhosis, lepromatous involvement of these organs, or passive congestion to account for the enlarged livers and spleens.

Elevation of the serum globulin fraction occurs in lepromatous leprosy per se, and when this disease is complicated by amyloidosis these changes persist or become more exaggerated, so that this finding likewise has been of little value in establishing the diagnosis of amyloidosis, although all cases of clinical amyloidosis have had elevated serum globulins.

Table 2 is the summary of the pertinent clinical and autopsy information obtained from 20 consecutive deaths at Carville. Nine of these cases died as a result of amyloidosis which was confirmed by autopsy findings. Case 16 showed minimal amyloidosis of the kidneys at autopsy, but during life had not had proteinuria, and had died from an unrelated cause. Cases 1 and 10 undoubtedly had amyloidosis, because of the 100% Congo red absorption in one hour and a supporting clinical picture, but as autopsies were not performed they are excluded from the autopsy correlation in the following discussion. The eight remaining cases had had Congo red tests performed, but died from causes other than amyloidosis. The absence of amyloid was substantiated by the postmortem findings.

All 10 cases with amyloidosis had lepromatous leprosy, eight having a moderate degree and two minimal involvement. Three of the 10 cases had had chronic trophic ulcers, with or without secondary infection, which might have accounted for the amyloidosis, and the remaining cases had no disease commonly associated with secondary amyloidosis, with the exception of lepromatous leprosy. Of the eight cases which were autopsied and found not to have amyloidosis, two had tuberculoid leprosy and six lepromatous leprosy.

Of the total 20 cases, the duration of leprosy varied from two to 35 years, with a mean of 15.03 years. In the 10 cases of proved amyloidosis the duration of leprosy ranged from two to 35 years, with an average of 7.6 years; however, it is difficult to place too much significance on this last figure, because in cases 6 and 17 it was necessary to rely completely on the patients' information, and they appeared clinically to have had leprosy for a longer period of time than they stated in their histories.

The results of skin tests for acid-fast bacilli over at least a two year period preceding their death in the 10 cases who died with amyloidosis were as follows: one was negative; two showed only rare acid-fast bacilli; two showed a minimal number; there were moderate numbers in two, and numerous organisms in three. All cases had been on sulfone therapy (either sulfoxone sodium or glucosulfone sodium) for at least a year preceding death.

Of these same 10 cases, three had had no erythema nodosum leprosum, three had had minimal amounts, and four had had a moderate amount of this syndrome which is seen rather frequently in leprosy.

In the 10 cases of amyloidosis proved at autopsy, the first sign to suggest this diagnosis clinically in nine of the 10 cases was the onset of pro-

TABLE 2

Correlation of Congo Red Test in Secondary Amyloidosis With the Clinical Picture and Autopsy Findings (20 Cases)

Case	Age	Type and Degree of Leprosy	E.N.L.†	*Myco. leprae* Skin Test	Duration of Leprosy (years)	Proteinuria, Date of Onset	Congo Red Percentage and Date Performed	Date of Death	Amyloidosis at Autopsy: Organs Involved
1. 2010	40	L_2N_1*	+++	++	8	Oct. 1951	100% Feb. 1952	May 1952	No autopsy
2. 401	65	L_3N_3	+−	++	35	Nov. 1948	65% Mar. 1952	Oct. 1952	Liver, spleen, adrenals, stomach, kidneys
3. 1322	46	L_3N_2	+	+	20	June 1944	34% July 1952	Oct. 1952	Spleen, kidneys, adrenals
4. 1356	59	L_1N_1	0	−	25	Jan. 1947	21% Oct. 1952	Nov. 1952	No amyloidosis
5. 2124	40	L_2N_2	+−	++++	16	July 1952	95% Oct. 1952	Jan. 1953	Adrenals, kidneys
6. 2110	71	L_3N_1	++	+++	4	Dec. 1952	77% Dec. 1952	Jan. 1953	Spleen, liver, adrenals, kidneys, lymph nodes, stomach
7. 1979	60	L_2N_2	+−	+	5	Dec. 1948	52% Oct. 1951 59% Feb. 1952	Mar. 1953	No amyloidosis
8. 2037	40	L_3N_3	++	+++	18	June 1951	100% Mar. 1952	Mar. 1953	Spleen, liver, adrenals, kidneys
9. 1914	50	L_2N_1	++	++	16	Dec. 1949	85% June 1951	Sept. 1953	Spleen, liver, adrenals, kidneys, pancreas, pituitary
10. 2168	26	L_3N_2	++++	++++	2	July 1953	17% Feb. 1952 100% Aug. 1953	Sept. 1953	No autopsy
11. 1338	70	L_1N_3	0	−	15	—	10% Feb. 1952	Dec. 1953	No amyloidosis
12. 2113	50	T	0	−	5	Mar. 1951	52% Oct. 1952	Feb. 1954	No amyloidosis
13. 2226	77	T	0	−	32	June 1953	55% Jan. 1953 45% Jan. 1954	Mar. 1954	No amyloidosis
14. 1702	57	L_3N_3	0	+	23	—	40% June 1954	July 1954	No amyloidosis
15. 1998	63	L_2N_1	++	++++	23	Aug. 1948	62% May 1953 60% May 1954	July 1954	Spleen, liver, adrenals, kidneys, pancreas, pituitary
16. 1113	81	L_3N_3	0	−	24	—	54.5% Jun. 1953	Aug. 1954	Kidneys—minimal
17. 2184	60	L_3N_1	+	++++	2	July 1954	93% July 1954	Sept. 1954	Spleen, liver, gallbladder, kidneys, adrenals, thyroid, ileum
18. 1985	92	L_1N_3	0	+	9	—	24% Sept. 1954	Oct. 1954	No amyloidosis
19. 1311	67	L_2N_3	0	+	18	Feb. 1951	42% Feb. 1952 48% Jan. 1954 97% Jan. 1955	June 1955	Spleen, liver, gallbladder, pancreas, kidneys—severe; adrenals, pituitary, thyroid, stomach—minimal; submaxillary gland—M.
20. 2063	71	L_2N_1	+++	++++	6	—	58% Oct. 1952	Feb. 1955	No amyloidosis

* Lepromatous—N T—Tuberculoid.
† Erythema nodosum leprosum.

teinuria, while in the other case the amyloidosis was found at autopsy to involve the kidneys to a minimal extent. This case had never had proteinuria and died from a cause unrelated to amyloidosis.

A Congo red test was performed on the nine cases with both amyloidosis and proteinuria from 1 to 69 months after the onset of the proteinuria (mean 31.66 months). The dye absorbed varied from 34 to 100% in one hour, with a mean of 76.05%. Case 15 had a Congo red test of 62% absorption 57 months after the onset of proteinuria, and the test was repeated in 69 months and found to be 60%. Case 19 showed a Congo red absorption of 42% 12 months after the onset of proteinuria, 48% in 40 months, and 95% in 47 months.

Of the eight cases who did not have amyloidosis at autopsy, the Congo red absorption varied from 10 to 59%, with a mean of 38.75%. Four of these non-amyloid cases had proteinuria during life, and of these four the Congo red absorption varied from 21 to 59%, with a mean of 44.25%. The test was performed from seven to 69 months after the onset of proteinuria, with a mean of 33.25 months. At autopsy either arteriolar nephrosclerosis, chronic pyelitis and cystitis, or chronic prostatitis was found to be the basis of the proteinuria.

The proteinuria in the proved amyloid cases occurred from two to 31 years after the onset of leprosy, with a mean of 13.66 years. The amyloid involved the kidneys in all cases, the adrenals in nine cases, the spleen in eight, the liver in seven, the pancreas, stomach and pituitary in three, the gallbladder and thyroid gland in two, and the submaxillary salivary gland, and lymph nodes in one. Of the 10 deaths directly related to amyloidosis, all showed severe amyloid nephrosis, and the Congo red absorption varied from 34 to 100%. Of the eight deaths not caused by amyloidosis and not showing amyloidosis at autopsy, the Congo red test varied from 10 to 59% absorption. All the amyloid deaths with from four to 10 organs involved had at least two involved extensively, and their Congo red tests showed 60 to 100% absorption in one hour. In the two amyloid deaths with two and three organs involved, the Congo red absorption was 95 and 34%, respectively. The one case of minimal renal amyloidosis who died from an unrelated cause had a Congo red absorption of 54.5% in one hour.

These 20 reported cases demonstrated what has been the general experience with amyloidosis at Carville, namely, that the Congo red test showing absorption above 80% in one hour is good evidence of amyloidosis; in the cases with Congo red absorption of from 40% to 80% the diagnosis cannot be made from this test alone, but can frequently be supported or proved from the clinical picture, and perhaps by liver biopsy and the study of the serum protein fractions. A Congo red absorption below 30% is strong evidence against the diagnosis of secondary amyloidosis.

Experience at Carville shows that amyloidosis resulting from leprosy per se occurs only in the lepromatous form of the disease, generally in the

moderately advanced cases and in cases of at least two years' duration. The positive skin scrapings merely signify the activity of the disease, and the onset of amyloidosis may occur after the disease is clinically arrested as judged by routine skin scrapings. The relationship of erythema nodosum leprosum reactions and amyloidosis is interesting and, as noted, seven of the 10 cases of proved amyloidosis at autopsy had had this complication during their illness. It is our impression that cases who develop a severe form of this syndrome have a tendency to develop amyloidosis, but further observations are necessary before this correlation can be substantiated. After the onset of proteinuria the average duration of life was 38.33 months, with a fairly wide range above and below this figure, and this also correlates with the general experience here at Carville. Renal involvement occurred in all

TABLE 3

Studies of Blood Protein and Lipoid Fractions in Lepromatous Leprosy With and Without Proteinuria

Congo Red, Per Cent Absorption	Serum Proteins, gm. per cent						Phospholipids, mg. per cent	Cholesterol, mg. per cent	Polysaccharide, Coleman units
	Total Protein	Albumin	Globulin	α	β	γ			
30 Cases With Proteinuria									
Minimum 29	3.6	0.5	1.9	0	0.4	0.1	130	120	10
Maximum 100	7.0	4.1	4.9	2.1	2.2	2.0	360	850	45
Average 69.7	5.9	2.8	3.1	0.9	1.6	0.9	203	243	30
30 Cases Without Proteinuria									
Minimum 0	5.3	2.2	1.3	0.3	0.4	0.1	130	152	15
Maximum 75	6.8	4.4	4.0	1.7	1.6	2.1	262	316	34
Average 34.6	6.0	3.4	2.6	0.9	0.8	0.8	201	228	23

cases and was the cause of death. The adrenals are involved nearly as frequently, but clinical adrenal insufficiency is rare and did not occur in any of the reported cases.

The correlation between the Congo red absorption and the degree of amyloid involvement is poor, but it is frequently found that by doing serial Congo red tests the test approaches 100% absorption prior to death, as demonstrated in case 19. No untoward reactions have been recorded in the cases that have had multiple Congo red tests performed.

Table 3 shows that, of the 30 cases with proteinuria, 15 had Congo red absorption of from 29 to 60%, and 15 from 60 to 100%. Of the 30 cases without proteinuria, 28 had Congo red absorption of from 0 to 60% and two cases had 73.9 and 75%, respectively. The abnormal findings are as follows:

	Cases With Proteinuria		Cases Without Proteinuria	
	Congo Red Absorption		Congo Red Absorption	
	29–60% No. of Cases	60–100% No. of Cases	0–60% No. of Cases	60–100% No. of Cases
Hyperglobulinemia	6	11	6	2
Increases in globulins alpha	3	6	9	1
Increases in globulins beta	11	12	6	2
Increases in globulins gamma	2	4	9	0
Increase in cholesterol	4	5	3	0
Increase in polysaccharides	5	8	3	1

There were no cases in either group of 30 who showed an increase in all three protein fractions of alpha, beta and gamma globulin. Of the 30 cases without proteinuria, the gamma globulins were found to be low in 14. In the group with proteinuria, the gamma globulins were low in seven of the cases who had Congo red absorption of from 29 to 60%, and in those cases who had Congo red absorption of from 60 to 100%, nine cases showed the gamma globulins to be below the normal range.

With few exceptions, the blood protein findings follow a definite pattern which varies quantitatively, depending upon the duration and severity of leprosy. In the course of the disease, even before there is any presumptive evidence of amyloidosis, certain changes in the blood proteins usually occur. The total serum proteins may be normal or decreased, and the serum globulins may show a perceptible increase, the serum albumin decreasing so that the albumin-globulin ratio becomes inverted. Any of the protein changes may be present, irrespective of the duration of amyloidosis; and in the same subject the total serum proteins and its albumin and globulin fractions may display significant quantitative fluctuations on different occasions, although the inversion of the albumin-globulin ratio will persist. Liver function tests, such as thymol turbidity and cephalin cholesterol flocculation, were positive in a number of cases, but this dysfunction may be as a result of the disturbed protein metabolism. Serum phospholipids were within the normal range. Cholesterol was found to be variable. Increases were noted in cases with or without evidence of amyloidosis. However, in lipoid nephrosis with 70 to 100% Congo red absorption the cholesterol content was found to be as high as 900 mg. per 100 c.c. A lowering of the cholesterol content of the serum seems to be proportionate to the gravity of the disease in advanced lepromatous leprosy. Serum polysaccharides likewise were variable; increases paralleled the extent of the disease. It has been suggested by Seibert [27] that serum polysaccharides increase in diseases characterized by tissue destruction or acute inflammations.

Observations of the Effect of Hyaluronidase on Secondary Amyloidosis

Case 2203. A 28 year old white female with lepromatous leprosy of three years' duration was admitted to Carville in December, 1952. Laboratory studies at that time were within normal limits except for very active leprosy (Lucio type) and a slight decrease in the total proteins, with marked albumin-globulin reversal. She showed considerable clinical improvement on sulfoxone sodium (Diasone) therapy and in November, 1953, returned to her home on a 30 day leave, but did not return until March, 1954. At this time weight loss was evident, skin tests were strongly positive for acid-fast bacilli, and she was having severe nerve pains in both lower extremities, associated with frequent reactions of acute erythema nodosum leprosum. Other studies were similar to the findings described above. Sulfoxone sodium therapy was reinstituted and she began to show improvement, except for the inability to gain weight and the development of polyuria and nocturia. In May, 1954, proteinuria began, 1 to 4 gm. of protein per 100 c.c., the spleen was found to be palpable two fingerbreadths below the left costal margin, and the liver was enlarged three fingerbreadths below the right costal margin. A Congo red test showed 100% dye absorption in one hour, the urine being negative. Her total protein was 5.6 gm.; albumin, 1.6; globulin, 4.0. A phenolsulfonphthalein test showed 26% excretion in 15 minutes and a total of 51% in two hours. A maximal urea clearance was 62% of average normal function. Urine showed concentration to 1.018; nonprotein nitrogen was 54 mg.%; creatinine, 0.8. Liver biopsy was performed on June 30, 1954, with a Vim-Silverman needle. The specimen showed extensive amyloidosis between hepatic cells and the lumina of the sinusoids; in some areas this material was as thick as one-half the diameter of the hepatic parenchymal cells, and the material appeared to be compressing the hepatic cells and narrowing the lumina of the sinusoids. At this time her hemoglobin was 9 gm.; red blood cells, 3,900,000; white blood cells, 13,600, predominantly polymorphonuclear; prothrombin time, 100% of normal; cephalin-cholesterol flocculation, 4 plus; thymol turbidity, 7 units. On December 1, 1954, hyaluronidase * was started, with an intravenous dose of 4,500 turbidity units (1,000 T.U. equal 1 mg.), and this was increased in daily increments until on the fifth day she was receiving 45,000 turbidity units. This dose was continued daily for an additional five days. On April, 1955, a similar course of hyaluronidase was given, except that the total amount, equal to 250 mg. of testicular hyaluronidase, was given in divided doses over a five day period. A summary of the protein and lipoid fractions of the serum during this course of therapy is shown in table 4. Quantitative urine protein determinations have continued to show between 1 and 3 gm. of protein per 100 c.c. of urine daily. A repeat Congo red test four days after the hyaluronidase therapy showed a 100% dye absorption in one hour, the urine being negative for Congo red. Following the first course of hyaluronidase the liver and spleen remained enlarged to a degree similar to the pretreatment size. During the second course of hyaluronidase the patient ran a fever as high as 101° F. daily, and there was an increase in her proteinuria and a clinical decrease in the size of the liver and spleen as compared with the findings on November 30, 1954, before start of therapy.

The rationale for using hyaluronidase in this patient was based on the assumption that amyloid is probably a mucopolysaccharide protein complex and perhaps related to hyaluronic acid; however, Meyer [28] showed that in vitro neither amyloid nor para-amyloid is digested by testicular hyalu-

* The hyaluronidase used was supplied by Dr. G. E. Farrar, Jr., of Wyeth Laboratories.

TABLE 4

Protein and Lipoid Fractions of the Serum During the Course of Hyaluronidase Therapy

	Protein Fractions						Lipoid Fractions			
	Protein*	Albumin	Globulin	α	β	γ	Phospholipid†	Mucoprotein	Cholesterol	Polysaccharide‡
11/30/54 Pretreatment results	5.0	1.6	3.4	1.8	1.0	0.6	197.5	3.1	315.0	35.0
12/6 Sixth day of treatment	5.4	1.6	3.8	2.8	0.5	0.5	125.0	3.0	252.0	25.0
12/13 Following completion of first course of therapy	5.6	1.6	4.0	1.65	1.95	0.40	200.0	2.8	240.0	25.0
3/22/55 Three months after therapy	5.6	2.5	3.1	0.8	1.2	1.1	170.0	2.8	260.0	35.0
4/5 Pretreatment of second course of therapy	6.0	2.4	3.6	1.6	1.0	1.0	250.0	3.0	270.0	33.0
4/8 Three days following therapy	6.0	1.7	4.3	1.9	1.8	0.6	300.0	3.0	350.0	45.0
4/11 Completion of therapy	5.7	2.1	3.6	1.7	1.2	0.7	247.5	2.8	222.0	30.0
5/3 Three weeks following second course of therapy	5.8	2.0	3.8	1.3	1.3	1.2	212.0	2.6	220.0	31.0

* Expressed in grams per 100 c.c.
† Milligrams per 100 c.c.
‡ Coleman units.

ronidase, and therefore apparently not by hyaluronic acid. In animal experiments it has been shown that antibodies to hyaluronidase develop when large doses are used intravenously after a period of approximately 10 days, and because of this we limited our course of treatment to this period. Following a three month rest period a second course of hyaluronidase was given because it was thought that, due to its weak antigenic properties with this rest period, the effects of hyaluronidase would not be inhibited by antibody formation. Protein fractionations showed no significant change during or immediately after the hyaluronidase, but the three month follow-up pattern is of interest in that the alpha fraction of the globulin was normal and the gamma fraction had improved; however, clinically there was no demonstrable change in the patient's amyloidosis. During the middle of the second course of therapy there was a definite increase of the beta fraction of the globulin, with a decrease in the gamma fraction. Of perhaps even more interest is

the rise in the polysaccharide fraction during this same period, and its return to normal following the course of hyaluronidase. The increase in proteinuria during the second course of hyaluronidase was definite, but unfortunately a breakdown of this protein was not done. Likewise, the clinical decrease in size in the hepatosplenomegaly is of interest, but no conclusions are being drawn at this time. The interpretation of this entire project is not clear at present, but subsequent courses of hyaluronidase are planned in this case and perhaps in similar cases.

Experiences with Liver Biopsy in the Diagnosis of Early Secondary Amyloidosis

In view of the definite amyloid picture obtained on liver biopsy in the patient just described, the possibility was considered of using this method for establishing the diagnosis earlier in the course of the disease, before proteinuria and a diagnostic Congo red test occurred.

The first case was a 53 year old female with lepromatous leprosy who developed polyuria with intermittent proteinuria, enlarged liver and spleen, 25% Bromsulphalein retention, reversal of the albumin-globulin ratio, and a Congo red test of 21% dye absorption. Liver biopsy showed typical portal cirrhosis and no evidence of amyloidosis.

The second case was a 54 year old male with lepromatous leprosy who, during an acute reactive phase of his disease, developed an enlarged spleen and liver that did not subside with the reaction, which is the usual course. There was no proteinuria, and Congo red absorption was 17%. The albumin-globulin ratio was decreased, and a moderate hypochromic microcytic anemia developed. Liver biopsy revealed miliary lepromata of the liver, but no evidence of amyloidosis.

These two cases were clinically suggestive of early amyloidosis, although the negative Congo red test and the absence of persistent proteinuria did not support this impression, and this was substantiated by the negative liver biopsies. These two cases therefore failed to support our original hypothesis that liver biopsy would help to establish the diagnosis of early secondary amyloidosis, but two cases do not prove or disprove the possibility, and more biopsies would be needed to come to any conclusions. In view of the potential danger of the procedure, it has not seemed warranted to biopsy more patients unless a clear-cut indication arises; however, it is felt that in an occasional patient liver biopsy might be helpful in establishing the diagnosis of secondary amyloidosis when the Congo red test is borderline and/or the proteinuria is just beginning or is intermittent.

Discussion

The clinical features of secondary amyloidosis of leprosy are quite uniform regarding specific organ involvement, e.g., kidney, spleen, liver, adrenal,

gastrointestinal tract and pancreas. There is a poor correlation between the degree of leprosy and the development of amyloidosis. The usual sequence of events begins with proteinuria, which is progressive and leads to hypoproteinemia, enlargement of the liver and spleen, nitrogen retention, anemia and death. Regarding renal involvement, hypertension is rare and, when present, is usually due to an underlying nephrosclerosis rather than a result of the amyloidosis. The degree of renal involvement correlates well with the urinary concentration test, phenolsulfonphthalein excretion, nitrogen retention and, finally, retention of creatinine. The proteinuria consists largely of albumin, but also contains globulins. The urinary sediment contains varying numbers of hyaline, granular and waxy casts, and a marked pyuria is frequently present. Microscopic hematuria is occasionally noted in varying degree, but frank hematuria has not been observed in our series. As the hypoproteinemia becomes more marked, edema becomes prominent, particularly in the lower extremities. Terminally, pleural effusions are not uncommon, but significant ascites is unusual. The final picture is that of a lipoid nephrosis, with normal blood pressure, hypoproteinemia, elevated serum cholesterol, renal failure with a metabolic acidosis, and death. Jaundice is very unusual. Bromsulphalein excretion is usually within normal limits; however, flocculation tests are usually abnormal, which is felt to be due to the altered plasma protein rather than to primary liver parenchymal damage. The anemia is interesting because it has a great bearing on prognosis, and because it is possible to keep the amyloid nephrosis compensated until the anemia becomes extreme, at which time death is usually imminent. Amyloid has not been demonstrated in the bone marrow of these cases. Generalized depression in the marrow is similar to that in other cases of uremia. We have not observed a case of Addison's disease secondary to adrenal amyloidosis in this series, and it is reported to be rare. Gastrointestinal complaints in the form of epigastric pain, tenderness, nausea and vomiting are frequent in advanced cases. These symptoms are probably caused by a combination of findings, including uremia and the edema of the intestinal mucosa, and also to amyloid involvement.

The prognosis is very difficult to determine. Some cases have amyloidosis for many years, with moderate anemia and hypoproteinemia and some elevation in the nonprotein nitrogen, but it is the rule that once the urea nitrogen and creatinine become markedly elevated death is imminent, particularly if there is a fair degree of anemia, as described above.

Periodic blood transfusions and concentrated serum albumin are temporary measures which will tide the patient over for varying periods of time; likewise, attention to water and electrolyte balance, with correction of metabolic acidosis, is of great assistance in converting uncompensated renal disease into a compensated form and giving these patients varying periods of active life. However, in any particular case the outcome cannot be determined. ACTH and cortisone have likewise been of temporary

benefit, but even with long-term cortisone therapy there have been no indications that the amyloidosis progressed or that it had any beneficial effect on the removal of amyloid. Hyaluronidase in large doses has been tried in one case. We used crude liver, as recommended in the literature,[29] but failed to see any great beneficial effect from this therapy.

Summary

Secondary amyloidosis is the leading cause of death in lepromatous leprosy in this country. The mortality is directly caused by amyloid involvement of the kidneys, which occurred in 100% of this series. The diagnosis of this complication depends largely on the development of a persistent proteinuria, Congo red absorption, hepatosplenomegaly and, to a lesser degree, altered serum proteins and perhaps liver biopsy in selected cases. The correlation between the Congo red test and the degree of amyloidosis is poor, and unless this test shows 80 to 100% dye absorption in one hour the diagnosis cannot be made from this finding alone. Serum protein and lipoid changes occur in lepromatous leprosy per se, and in a study of the various protein fractions no consistent alteration occurred in cases complicated by amyloidosis. The average duration of life after the onset of proteinuria in amyloidosis was 38.33 months, with a fairly wide range above and below this figure. The development of anemia and a progressive elevation of the nonprotein nitrogen are unfavorable prognostic signs.

Summario in Interlingua

Amyloidosis secundari es le principal causa de morte in lepra lepromatose in le Statos Unite. Le mortalitate es causate directemente per un involvimento amyloide del renes. Isto occurreva in 100% del patientes del serie presente. Il has solmente un basse correlation inter le duration e le grado de lepra lepromatose e le disveloppamento de amyloidosis.

Amyloide es considerate como un complexo proteino-polysaccharidic con un tendentia a variar in composition. Il existe un relation inter amyloide e hyperglobulinemia o inter illo e un specific fraction del globulinas seral. Il es etiam possibile que il ha un connexion inter amyloide e un alterate structura de histos conjunctive e un disturbate relation de anticorpore e antigeno.

Le diagnose de amyloidosis secundari in lepra depende in grande mesura del sequente constatationes que es listate in le ordine de lor importantia: Proteinuria persistente; absorption de rubio congo, amontante in un hora a 60% e preferibilemente a 80%; hepatosplenomegalia e hyperglobulinemia, sin o con hypoalbuminemia, sin uniforme alterationes del fractiones de globulina. Alterationes de proteina e lipido seral occurre in lepra lepromatose per se, e nulle uniforme alterationes additional de iste genere esseva notate in casos complicate per amyloidosis. Tests serial con rubio congo attinge frequentemente resultatos proxime a 100% de absorption quando le morte es imminente, e isto mesmo in casos in que le resultatos initial esseva negative.

Le superviventia median post le declaration de proteinuria in casos de amyloidosis esseva circa 38 menses, con satis marcate variationes supra e infra iste valor. Le

disveloppamento de anemia e un progressive elevation del nitrogeno non-proteinic es signos disfavorabile pro le prognose.

A causa del possibile relation inter acido hyaluronic e amyloide, un patiente con amyloidosis avantiate esseva subjicite al administration de duo cursos intravenose de hyaluronidase. Cata un del cursos consisteva de circa 250 mg de hyaluronidase que esseva administrate in doses dividite in un periodo de cinque dies. Post iste therapia il habeva un tendentia de normalisation in le fractiones de globulina, e durante le periodo del therapia il habeva un augmento de polysaccharido. Studios additional es necessari pro determinar le signification de iste alterationes.

In casos de suspicion de amyloidosis in que le test a rubio congo esseva negative, biopsias hepatic esseva executate per medio del agulia de Vim-Silverman. Iste technica es de valor pro le differentiation de amyloidosis ab sever lepra lepromatose que involve le hepate.

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THE EARLY DIAGNOSIS AND NATURAL HISTORY OF CHRONIC LYMPHATIC LEUKEMIA *

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It is well known that chronic lymphatic leukemia may run a long and practically asymptomatic course. The classic picture of splenomegaly, lymphadenopathy, anemia and a very high leukocyte count is probably only a late phase in the natural history, but it is this stage of the disease that has received the most study. The pathologic processes at the inception of a disease are always the most interesting, yet there are few clinicopathologic data on chronic lymphatic leukemia in its early stages. This is probably because the opportunity to observe the course of leukemia before the disease has caused symptoms is necessarily rare.[1,2]

The nine cases of chronic lymphatic leukemia to be described were all first seen with presenting symptoms not attributable to leukemia, and are of interest because of the light they throw on the natural history of the disease. Three of the patients died from causes unrelated to leukemia in an asymptomatic phase of the disease, and autopsies were performed on two of them. Both lymph nodes and splenic biopsies were performed on another patient at a relatively early phase of the disease, and in three others lymph node biopsies were carried out at an early, intermediate and relatively late phase, respectively.

Methods

Contamination of the bone marrow aspirates by peripheral blood was excluded as much as possible by sucking off most of the blood by means of a fine Pasteur pipette and counting only along the cellular trails as described by Dacie.[2] Marrow sections were prepared from the aspirated material in six of the cases.

Smudge and basket cells were an almost constant feature of the peripheral blood smears, but as such cells may be artefacts they were ignored when differential white cell counts were performed. Platelet counts were performed by Lempert's [6] modification of Kristenson's [5] platelet counting tech-

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TABLE 1

Summary of Clinical and Hematologic Findings in Nine Cases of Chronic Lymphatic Leukemia

Case		Nodes	Spleen	Liver	Symptoms[1]	Hb. Gm.%	W.B.C. (thousands per cu. mm.)	Lymphocytes (thousands per cu. mm.)	Platelets (thousands per cu. mm.)	Marrow Lymphocytes (% of nucleated elements)
1	Nov. 1950	0	0	0	0	13.9	30	18	170	34
	June 1951	0	0	0	0	11.8	25	21	200	—
	Aug. 1953	0	0	0	0	11.8	35	24	180	—
	Feb. 1954	0	0	0	0	13.8	36	25	223	—
	April 1955	0	0	0	0	13.8	40	34	190	—
2	Dec. 1953	0	0	0	0	14.5	18	16	191	28
	June 1954	0	0	0	0	14.6	22	19	200	—
	Feb. 1955	0	0	0	0	14.0	26	21	180	—
3	Dec. 1950	0	0	0	0	12.7	28	15	220	31
	April 1951	0	0	0	0	12.1	38	26	—	—
4	Feb. 1954	0	0	0	0	14.8	63	60	142	29
5	Feb. 1954	+	0	0	0	14.0	40	30	262	40
	Nov. 1954	+	0	+	0	10.1	114	91	Plentiful	Very high
	Feb. 1955	+	0[2]	+	0	—	95	77	Plentiful	—
6	1947	+	0	0	0	—	—	—	—	—
	Feb. 1951	+	+	+	0	14.5	22	18.7	—	—
	March 1952	+	+	+	+	9.8	66	64.5	130	—
	June 1953	+	+	+	+	4.7	110	107	90	—
7	Oct. 1944	+	+	+	0	10.7	16	8	200	59
	April 1945	+	+	+	0	4.3	5	2.2	193	4
	July 1951	+	+	+	0	13.0	16	11.2		70
	Sept. 1952	+	+	+	0	10.8	32	29.8	160	—
	July 1953	+	+	+	+	8.9	111	109	120	—
8	Aug. 1955	+	0	0	0	13.8	20	15	220	32
9	Aug. 1955	+	+	+	+	12	28	23	180	35

0 Indicates no abnormality.
+ Indicates enlargement of organs or presence of symptoms.
— Indicates no observation.
[1] Attributable to leukemia.
[2] Felt on one occasion.

nic. The normal range in health by this method is approximately 150,000 to 350,000 per cubic millimeter.[2]

The nine cases to be described below were personally seen and examined by the author and satisfy all the accepted hematologic requirements for the diagnosis of chronic lymphatic leukemia. The hematologic findings in all nine cases are summarized in table 1.

CASE REPORTS

Case 1. A white male, aged 80, was admitted to hospital in November, 1950, with a large left hydrocele and symptoms of prostatic enlargement. A routine white

cell count was performed; chronic lymphatic leukemia was suspected, and this diagnosis was supported by the sternal marrow aspiration biopsy. The patient was followed up for four and a half years and, when last seen, was fit and well. The clinical and hematologic findings are summarized in table 1.

Comment: The consistently raised absolute lymphocyte count during the four year observation period, despite the consistent absence of signs and symptoms, makes the diagnosis of chronic lymphatic leukemia unequivocal.

Case 2. A white female clerk, aged 64, attended the skin out-patient department in December, 1953, with a generalized purpuric rash, most marked on the legs and arms. The rash had been present for one month. The clinical and hematologic findings are summarized in table 1. The skin rash improved with local treatment, and by April, 1954, had almost completely disappeared. It recurred, however, in June of the same year, and later improved, only to recur again, and the rash was still present when the patient was last seen, in February, 1955. Skin biopsy then showed perivascular inflammation and necrotizing arteriolitis; no leukemic infiltration was seen.

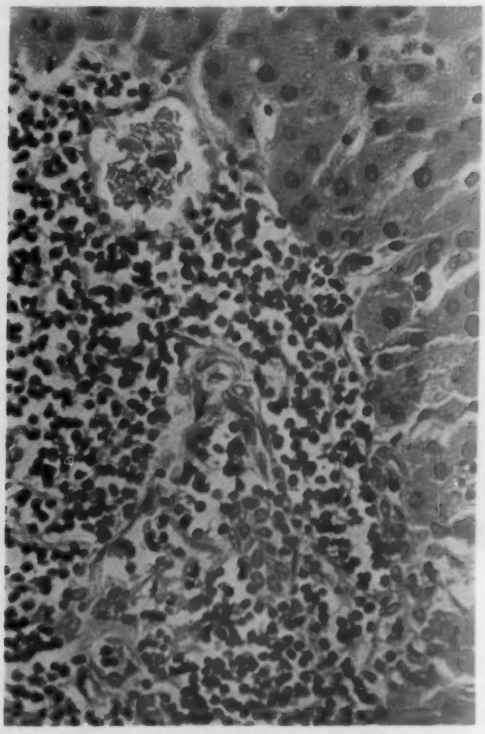

FIG. 1. *Case 4.* Section of liver taken at autopsy showing portal infiltration by lymphocytes. Hematoxylin and eosin. × 430.

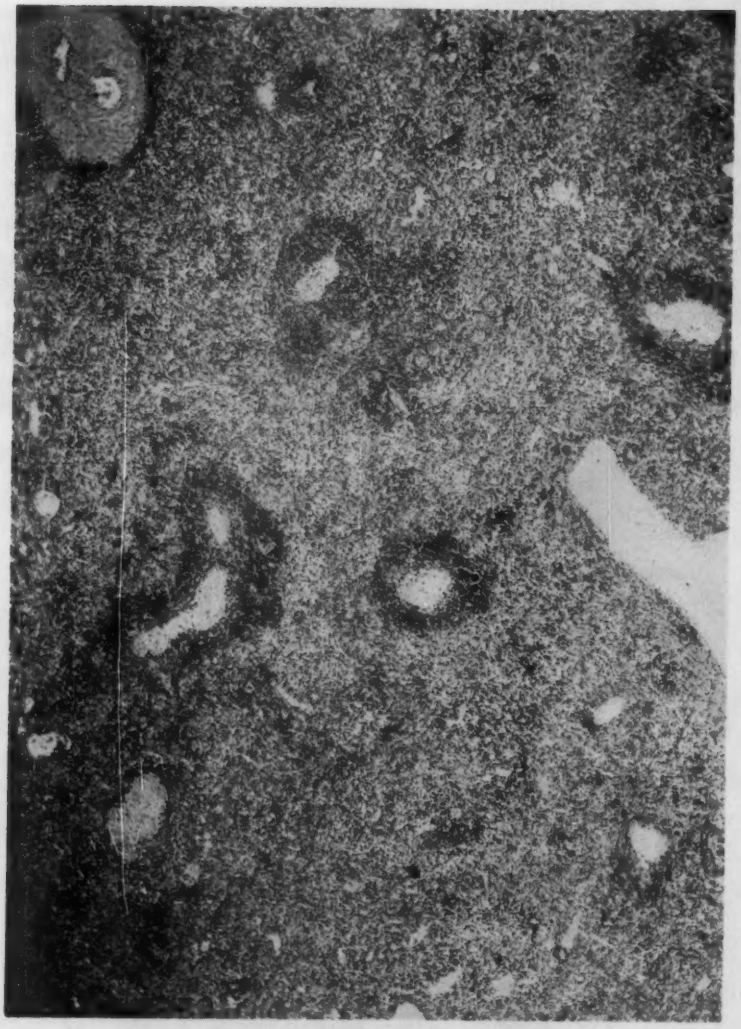

FIG. 2. *Case 4.* Autopsy specimen, section of spleen showing small, well demarcated malpighian follicles. No obvious lymphocytic infiltration of pulp. Hematoxylin and eosin. × 45.

Comment: Although the skin rash was the sign that led to the discovery of the leukemia, in the absence of thrombocytopenia and leukemic infiltration of the skin this sign cannot be attributed to the leukemic process.

Case 3. A retired white dentist, aged 76, was first seen in November, 1946, with symptoms of prostatic enlargement. In December, 1950, he was seen again and

was complaining of headaches and a dry mouth. His blood urea nitrogen was 68 mg.%. Shortly after admission to hospital he became confused. Signs of circulatory collapse appeared, and he developed pulmonary and urinary tract infections. The chronic lymphatic leukemia was discovered as a result of a routine leukocyte count, followed by a sternal marrow aspiration biopsy (table 1), and subsequent blood studies showed an essentially similar picture. The patient died at home six months later from bronchopneumonia and uremia. Permission for autopsy was not obtained.

Case 4. A white male, aged 75, was first seen in February, 1954, when he gave a six weeks' history of vomiting, dysphagia and loss of weight. A carcinoma of the lower end of the esophagus was diagnosed and confirmed by x-ray examinations. A routine white cell count, followed by a sternal marrow aspiration biopsy, showed the presence of an associated chronic lymphatic leukemia. There was no clinical splenomegaly, hepatomegaly or lymphadenopathy (table 1). The patient developed a chest infection and died 10 days after admission.

Summary of Autopsy Findings: Alimentary tract: Stenosing squamous cell carcinoma infiltrating lower end of esophagus. Lungs: Bronchopneumonia in right lower lobe. Bone marrow: The marrow cavity of the humerus was filled with grayish pink marrow and, on histologic examination, there was heavy lymphocytic infiltration. Liver: This was slightly enlarged and showed small grayish white nodules which

FIG. 3. *Case 5.* Section of liver taken at autopsy showing well marked portal infiltration by lymphocytes. Hematoxylin and eosin. × 100.

were just visible in the portal distribution; a single small metastasis was seen. Microscopy of the liver (figure 1) showed portal infiltration by lymphocytes. Spleen: This was of normal size and appeared unremarkable both grossly and on microscopic examination (figure 2). Lymph nodes: No enlarged lymph nodes were found; on microscopy, however, a small metastatic deposit of carcinoma was seen in one of the para-aortic nodes; the histologic appearances of the nodes were otherwise unremarkable.

Comment: The white cell count in this case was higher than the initial white cell counts in any of the other cases in this series, and it is tempting to attribute this finding to the associated carcinoma.

Case 5. A white male caretaker, aged 68, was admitted to the hospital in February, 1954, with a long history of cough which had become progressively worse each winter. On physical examination chronic bronchitic and emphysematous changes were found in the chest, and there was slight enlargement of the lymph nodes in his axillae and groins. The patient improved and was discharged one month after admission with the diagnosis of chronic lymphatic leukemia. Ten months later he was admitted to another hospital complaining of a cough and chest pain. On examination there was now a pleural rub, and fine râles were heard over both lung fields, most marked on the left side. Purpuric spots were seen on the chest and buccal membranes. The capillary fragility test was positive. The liver was moderately enlarged, and on one occasion the tip of the spleen was felt. The patient died on February 24, 1955. The hematologic and clinical findings are summarized in table 1.

Summary of Autopsy Findings: External examination: Slightly enlarged firm nodes in the axillae and groins. Respiratory system: Many irregular small nodular areas were scattered throughout both lungs; some appeared to be bronchopneumonic, while others were discrete and gray in color. Histologic sections showed the discrete nodules to be adenocarcinoma, probably bronchogenic in origin. Liver: This was slightly increased in size, and there appeared to be a general increased prominence of portal tracts. Microscopy showed marked portal infiltration with lymphocytes (figure 3). Spleen: The spleen weighed 440 gm. and was soft, and the cut surface showed loss of normal architectural outlines and was pinkish red and homogeneous in appearance. On microscopy the capsule was thickened. The malpighian follicles were small and poorly demarcated from the intervening pulp, which showed focal areas of reticulum cell hyperplasia and contained an excess of lymphocytes, plasma cells and histiocytes. Some of the sinusoids were dilated and filled with lymphocytes (figure 4). Lymph nodes: The hilar, para-aortic, splenic, porta-hepatic and supraclavicular nodes were all slightly enlarged and soft, with pale pink homogeneous cut surfaces. The largest nodes were in the hilar region and in the superior mediastinum, and measured up to 6 cm. in maximal diameter. On microscopy several of the hilar nodes contained deposits of adenocarcinoma. Neither the sinuses nor the follicles were prominent. The nodes in the para-aortic region, which did not appear to be involved by carcinoma, showed slight loss of their normal architectural markings. The few remaining follicles were small and lacked germinal centers, and there was an increase of medullary tissue with an excess of plasma cells and lymphocytes, the latter being the predominant cells; the reticulum cells were inconspicuous. There was no change in the fibrillary stroma or sinusoids. Mitotic figures were infrequent (figure 5). Bone marrow: The bone marrow taken from the vertebral marrow was hyperplastic and showed marked lymphocytic infiltration. Heart: Right ventricular hypertrophy. Kidneys: Bilateral chronic pyelonephritis with well marked lymphocytic infiltration; the larger part of this was attributable to the inflammation, but some may have been due to the leukemic process. The other organs were unremarkable.

Comment: The presence of an associated carcinoma in this and in the previous case is of interest. Beresford [1] found an associated carcinoma in 20 out of a series of 106 cases of chronic lymphatic leukemia; this incidence is higher than in other series [8, 10] and appears significant.

Case 6. An obese white male, aged 71, was seen in 1947 complaining of pains in his arms. He was found to have a prolapsed cervical disc and enlarged cervical nodes, and he improved with physiotherapy. A white cell count was not performed

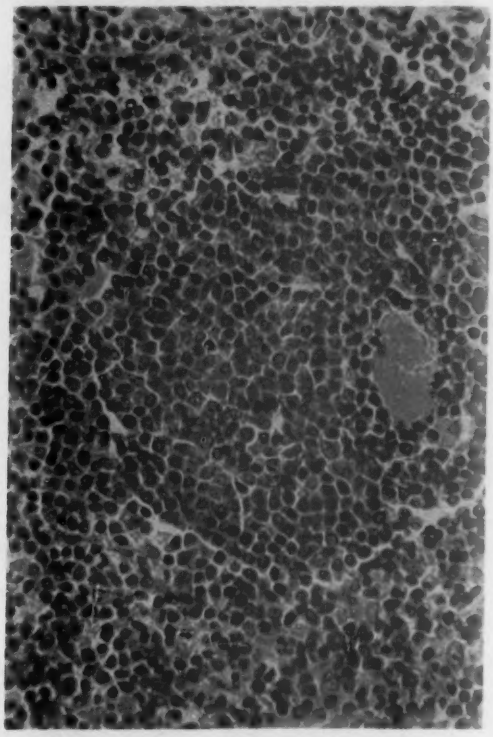

FIG. 4. *Case 5.* Section of spleen taken at autopsy. Malpighian follicle moderately well demarcated from the pulp, which shows mild lymphocytic infiltration. Hematoxylin and eosin. × 430.

at this time, and the patient was next seen in 1951, complaining of pain in his right shoulder. The clinical and hematologic findings are summarized in table 1. A biopsy of a node in the neck taken in 1951 showed loss of the normal architecture of the node and replacement by lymphocytes; it was reported as showing the changes of chronic lymphatic leukemia by the pathologist, who was unaware of the blood count and clinical findings. In view of this absolute histologic diagnosis and the peripheral blood picture (table 1), sternal marrow was not considered necessary. A year later the patient had gained some weight and his general condition was fair.

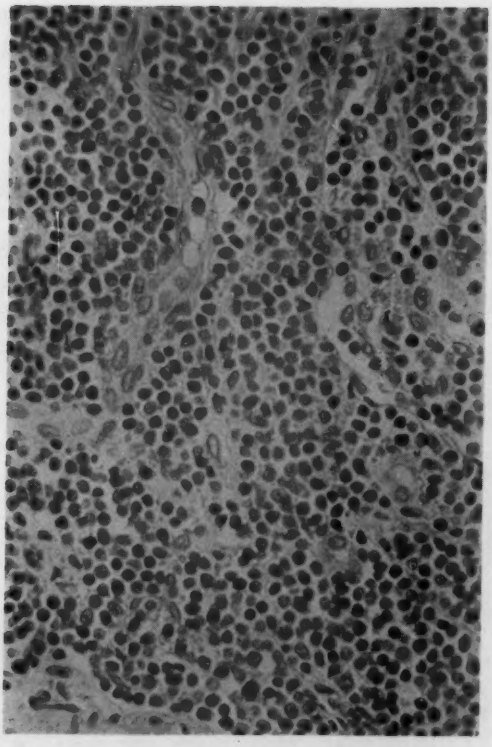

FIG. 5. *Case 6.* Section of para-aortic lymph node taken at autopsy showing relatively well preserved nodal architecture. Hematoxylin and eosin. × 430.

When last seen by the author, in June, 1953, he was in congestive heart failure due to severe anemia and had all the classic signs of chronic lymphatic leukemia. The patient died six months later at another hospital, where he had been receiving x-ray therapy during the last 12 months of his life.

Comment: Although no blood count was performed when the patient was first seen in 1947, the enlarged cervical lymph nodes suggest that an asymptomatic leukemia was present at this time.

Case 7. A white housewife, aged 50, was first seen in 1944 complaining of indigestion. Examination revealed splenomegaly, slight generalized lymphadenopathy and enlargement of the liver. The hematologic findings (table 1) were considered suggestive of chronic lymphatic leukemia. An exploratory laparotomy was performed because of a suspected gastric ulcer. At operation, an area of scarring in the lesser curvature was present but no actual ulceration was found; a biopsy was taken of the spleen, which was said to be seven times its normal size. This showed congestion of the pulp, with widely separated malpighian follicles, which were of normal size; no leukemic infiltration was present. The patient was then transferred to another teaching hospital, and here a lymph node biopsy was taken and reported

upon as follows by the professor of pathology: "The gland is the seat of a mild chronic inflammatory hyperplasia without any noteworthy disturbance of its architecture." During the next six months the patient had a number of gastric hemorrhages and was readmitted to the West London Hospital. A leukocyte count performed at this time was recorded as 5,000 per cubic millimeter, with 40% lymphocytes; the bone marrow showed only 4% of the nucleated cells to be lymphocytes. On the basis of these two findings, the original diagnosis of chronic lymphatic leukemia was abandoned. The patient responded to iron and blood transfusions and remained symptomless until 1951. She then complained of a recurrence of her earlier dyspeptic symptoms and was readmitted to the West London Hospital, where she was first seen by the author. On physical examination there were gross splenomegaly, hepatomegaly and slight generalized lymphadenopathy. She was slightly anemic (11.2 gm.%), with a moderately raised leukocyte count (16,000 per cubic millimeter, with 70% lymphocytes). The patient improved and remained symptomless until 1953, when she complained of a dragging sensation in her abdomen; all the important features of a classic case of chronic lymphatic leukemia were now present.

Comment: There can now be little doubt that this patient had chronic lymphatic leukemia when first seen in 1944; both the initial peripheral blood

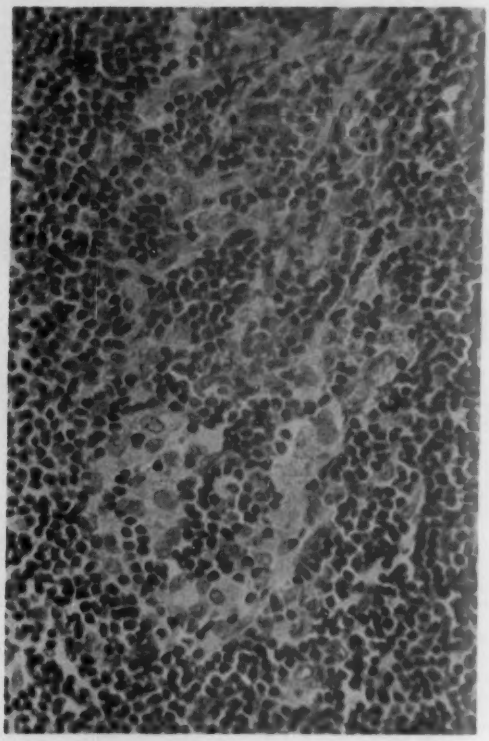

FIG. 6. *Case 8.* Lymph node biopsy showing intact nodal architecture. Hematoxylin and eosin. × 430.

and marrow reports support the diagnosis. The normal bone marrow and peripheral blood findings three months later, in the absence of treatment, are difficult to explain, and, unfortunately, further blood studies were not carried out until 1951. The anemia in 1947 is not attributable to the leukemic process, since it responded well to iron.

Case 8. A 58 year old white male furniture-maker was admitted to the North Carolina Memorial Hospital on August 3, 1955, with a nine months' history of fleeting

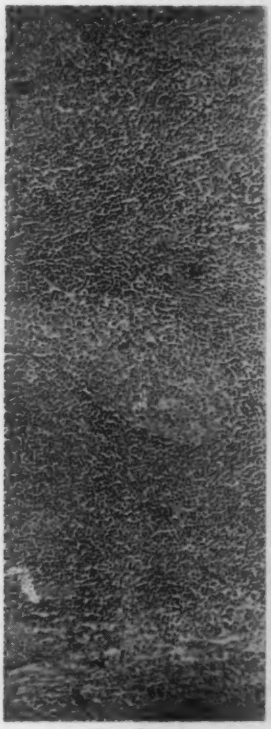

FIG. 7A

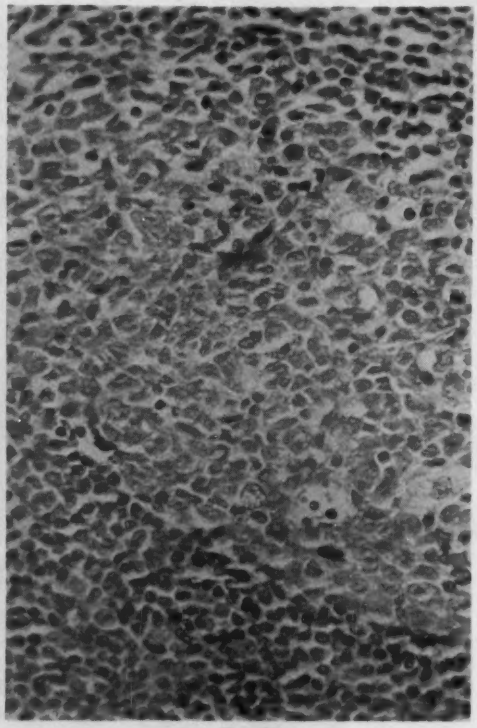

FIG. 7B

FIG. 7A. *Case 9.* Lymph node biopsy showing moderate preservation of normal architecture, with increase of lymphoid cells in the medulla. Note germinal center. Hematoxylin and eosin. × 93.

FIG. 7B. *Case 9.* The same germinal center. Hematoxylin and eosin. × 430.

ankle edema, progressive anorexia, lassitude and dizziness. On examination there were a few soft, discrete, palpable nodes, averaging 1 by 1 cm. in size, in the axillary and inguinal regions. One of the axillary nodes was biopsied and on gross examination had a whitish gray surface and was soft to palpation. The following histologic report (see figure 6) was given: "The normal architectural markings of the lymph node are intact. No germinal centers are present. The sinusoids are filled with somewhat enlarged reticulum cells. Evidence of neoplasia is not demonstrated." The

clinical and hematologic findings are summarized in table 1. No heterophil antibodies were demonstrated.

Case 9. A white male, aged 45, had been well until August, 1955, when bizarre behavior led to his admission to the State Mental Hospital. While under observation he developed pains in his right chest and stomach. Physical examination revealed discrete, shotty, easily palpable lymph nodes measuring 1 to 3 cm. in the clavicular, axillary and inguinal regions. The spleen extended three fingerbreadths below the left costal margin and the liver two fingerbreaths below the right costal margin. The heart and chest were normal. The margins of the left optic disc were blurred, and the left plantar reflex was extensor. The clinical and hematologic findings are summarized in table 1. A node biopsy (figures 7A and B) was reported as follows: "The general architecture of the node is fairly well preserved. The follicles appear to be normal in size and a few of these have small germinal centers. An overgrowth of lymphoid cells with occasional histiocytes and reticulum cells is noted in the medulla; mitotic figures are not seen. The capsule of the node and perinodal tissues are intact. There is no evidence of malignancy."

Comment: This patient had physical signs of chronic lymphatic leukemia when the diagnosis of this disease was first made. The leukemia was probably asymptomatic, and the neurologic signs and symptoms attributable to other causes. Leukemic infiltration of the brain is rarely seen in chronic lymphatic leukemia in the absence of thrombocytopenia or purpura. Chronic lymphatic leukemia differs from the other types of leukemia in this respect.

Summary of Hematologic Findings and Differential Diagnosis

At one time during the course of the chronic lymphatic leukemia the peripheral blood films in each of the nine cases were indistinguishable from one another. The total leukocyte count tended to vary from week to week by as much as $\pm$ 30%, but in the two cases followed over four years the lymphocyte count showed a definite upward trend. There was always a relative and absolute lymphocytosis; the only exception was the single white cell count performed in 1945 on case 7. The predominant cell type was the small lymphocyte, but large lymphocytes were almost invariably present at some time in each of the cases and sometimes constituted as much as 30% of the total lymphocytes. Lymphoblasts were rarely seen; at no time did they exceed 0.5% of the total leukocytes. Myelocytes, late normoblasts, Rieder cells and atypical lymphocytes resembling those seen in glandular fever were all seen in the stained films from time to time.

The bone marrows in the eight cases in which marrow biopsy was performed were very similar in appearance. The granulocytic series showed a slight shift to the left, with an increase in promyelocytic and myelocytic forms, but otherwise granulopoiesis was unaffected; erythropoiesis was either macronormoblastic or normoblastic. Scattered among these cells were foci of small lymphocytes which in all cases exceeded 25% of the total nucleated marrow count. Lymphoblasts were present in very small numbers, rarely exceeding 2% of the total nucleated counts. Megakaryocytes appeared to be present in either normal or slightly diminished numbers.

Dacie [2] gives the upper limit of normal for lymphocytes in aspirated bone marrow, based on various authors, as 20%. The marrow lymphocytosis in each of the eight cases was above this range, and the marrow sections, which were prepared from the aspirated material in six of these, showed that this lymphocytosis was a true one and not merely due to contamination with peripheral blood.

There are very few conditions, apart from chronic lymphatic leukemia, that give rise to marrow lymphocytosis; if acute infective lymphocytosis, a disease of children and young adults, and infectious mononucleosis can be ruled out, a marrow lymphocytosis of over 20%, together with an absolute lymphocytosis in the peripheral blood, may be considered almost pathognomonic of lymphatic leukemia. The persistence of the peripheral blood lymphocytosis over a period of several months makes the diagnosis unequivocal.

Chronic lymphatic leukemia is often mistaken for Banti's syndrome when there is splenomegaly with a relatively low leukocyte count. This mistake, however, should rarely be made, for while there is often a relative lymphocytosis in Banti's syndrome, the absolute lymphocyte count rarely, if ever, exceeds 4,000 per cubic millimeter. A more serious error is to mistake the acute variety of lymphatic leukemia for the chronic type. Anemia and thrombocytopenia are usually marked at an early stage of acute leukemia, but even in the absence of both these findings the differentiation can readily be made from a peripheral blood film, since true lymphoblasts rarely exceed 1% in the chronic disease. However, in an overstained blood film the lymphoblasts closely resemble mature small lymphocytes and may be mistaken for these cells; slight understaining, on the other hand, brings out the nuclear pattern and differentiation then becomes relatively simple.

Discussion

The lymph nodes at the stage when chronic lymphatic leukemia is usually seen are discrete, small, firm, painless and only moderately enlarged; they rarely if ever ulcerate or involve neighboring organs. According to Wintrobe,[11] it is exceedingly rare for adenopathy to be absent, and in four of 16 cases of chronic lymphatic leukemia observed by Wintrobe and Hasenbush [12] from an early stage, glandular enlargement was the sign which first attracted attention. In seven of their remaining cases, however, lymphadenopathy was slight, and in one of these only axillary nodes were palpable.

In four of the nine cases under review (cases 1, 2, 3, 4) there was no lymphadenopathy, while in another (case 5) small nodes were barely palpable in the axillae and groin. In these five cases the leukemia was quite unexpected, and was discovered as a result of a routine leukocyte count. McGavran [7] reported a similar case, first diagnosed in 1911; for seven years this patient had no palpable nodes. The remaining four patients (cases 6,

7, 8 and 9) in the present series all had palpable nodes when first seen. The diagnosis of chronic lymphatic leukemia in one of these (case 6) was made four years later, when splenomegaly and hepatomegaly were advanced. The lymph node biopsy in this case showed the classic changes of chronic lymphatic leukemia, with complete replacement of the normal architecture by a monotonous collection of lymphocytes.

Cases 4 and 5 died 10 days and 15 months, respectively, after the diagnosis of leukemia, the former from an associated carcinoma of the esophagus and the latter from an associated carcinoma of the lung with bronchiectasis. Neither of these patients had any symptoms positively attributable to leukemia, and no enlarged nodes were found at autopsy in case 4. Case 5, however, was found to have generalized lymphadenopathy. The nodes in both these cases showed no changes pathognomonic of leukemia, and without any clinical pathologic data a possible diagnosis of chronic lymphatic leukemia in case 4 would not have been considered. There was extensive bone marrow involvement by lymphocytes in both these cases, and the livers, even at this early stage of the disease, showed well marked portal infiltration which was apparent on gross examination. The lymph nodes taken during life from cases 7, 8 and 9 also showed no changes pathognomonic of leukemia, and all three were, in fact, reported as showing changes of reactive hyperplasia; no mention of lymphatic leukemia appeared in the reports.

The spleen was examined in three cases. In one of these (case 4) the spleen was of normal size and showed no histologic changes apart from congestion; in another (case 7), the spleen appeared to be approximately seven times its normal size but also showed no changes suggestive of leukemia. In the third, however (case 5), there were changes possibly attributable to leukemia.

In the five cases in which the lymph nodes showed no obvious leukemic changes, both the peripheral blood and bone marrow pictures were already pathognomonic of chronic lymphatic leukemia. Lymph node biopsy in an early case of chronic lymphatic leukemia would therefore appear to be of little help and may, in fact, be misleading in excluding the correct diagnosis. This is contrary to the view of Forkner.[3] It must not be inferred from the present findings that the lymph nodes in early lymphatic leukemia show no departure from normal, but only that diagnosis by a competent pathologist is usually, if not always, impossible in the early stages of the disease.

When the leukemia was first discovered no anemia was present in six of the nine cases under review, while in a further two (cases 3 and 9) the anemia was not significant. The anemia in the remaining case (case 7) was presumably attributable to gastric bleeding and not to leukemia, for it subsequently responded to treatment without specific antileukemic therapy. In Wintrobe and Hasenbush's [12] series of 16 cases, no anemia was initially present in six, and moderate anemia (10.1 gm.) was present in another; the hemoglobin levels in the remaining cases were not recorded.

It is noteworthy that the white blood counts in all but one of the present series of nine cases, 14 out of 16 of Wintrobe and Hasenbush's [12] series, and McGavran's [7] case were initially below 45,000 per cubic millimeter. The white cell count in cases 1, 6 and 7, who were followed up for a number of years, while varying from time to time showed a definite upward trend. In two of these patients the count eventually exceeded 100,000 per cubic millimeter. The same upward trend is seen in McGavran's patient, while Richter [9] has also observed, in a patient with chronic lymphatic leukemia, a gradual increase of white cells from 9,000 per cubic millimeter, with 60% lymphocytes, to 118,000 per cubic millimeter, with 95% lymphocytes, during a period of nine years; there was no anemia during this time. In two of my cases (cases 6 and 7), the terminal rise in the white cell count was associated with a fall in the hemoglobin and platelet count, and these patients then had all the classic features of chronic lymphatic leukemia. It would appear, therefore, that a low white cell count is an important feature of early lymphatic leukemia. This point is stressed, since a poor prognosis has been attributed to cases of chronic lymphatic leukemia with low white counts, one author [4] stating that such patients die within a year. The white cell count must not, of course, be used alone as the prognostic gauge, but must be considered along with the other hematologic findings and clinical picture, since a blood count taken for the first time during a spontaneous remission may give an unduly optimistic picture, while a fall in the white cell count is not infrequently a terminal event.

It is probable that the first detectable change in the evolution of chronic lymphatic leukemia is a relative and slight absolute lymphocytosis (Pinkus' sign), but there is no evidence as to whether this lymphocytosis is associated with focal lymphocytic involvement of the bone marrow. The present findings suggest that such focal involvement is present at least at a very early stage of the disease, if not at its inception. The spleen and lymph nodes may enlarge slightly, but often are not palpable for many years and show little histologic departure from normal, for while lymphocytic infiltration almost certainly occurs, this cannot be recognized against the general background of lymphoid tissue. Portal infiltration of the liver appears to be an early feature. This "silent" phase probably lasts several years, but soon signs of the disease, which is still symptomless, appear. Enlargement of lymphoid tissues, especially the tonsils, now becomes clinically obvious. The hemoglobin and platelet count are normal, and the white cell count remains relatively low. The marrow shows focal lymphatic involvement, but the hemopoietic reserves are adequate for normal demand. This is the stage of the disease frequently mistaken for Banti's syndrome, and this phase of signs without symptoms may also continue for several years. Eventually, however, the hemopoietic reserves become exhausted: the hemoglobin level and platelet count begin to fall, and the white cell count, which has been increasing slowly over a period of many years, rises to a high level. The

classic picture of chronic lymphatic leukemia has been reached, and the patient enters the terminal stages of a very long and protracted disease and has not many more months to live. Skin rashes and other symptoms suggestive of leukemia may occur at a relatively early phase of the disease, but such lesions should not be attributed to leukemia unless actual leukemic infiltration or thrombocytopenia is demonstrated, even though the symptom in the first place led the physician to suspect the leukemia.

The course as outlined above is that of a case unmodified by treatment; only one patient in the present series (case 6) received antileukemic treatment, and this was given one year before death. Similarly, McGavran's patient first received treatment 15 years after the diagnosis was first made. There have been many papers on the effect of specific treatments, such as x-rays and urethane, on chronic lymphatic leukemia; some of these are favorable, others indicate that little can be expected apart from alleviation of symptoms due to enlarged viscera or lymph nodes, and that life is not prolonged. In most of these reports, however, specific treatment was started relatively late in the course of the disease, usually in the classic or terminal phase. There are no data on the effect of treatment on the silent phase of the disease, and most authorities do not recommend treatment in the asymptomatic phases.

There are of course many factors that must be considered in giving a prognosis in a patient with chronic lymphatic leukemia. The disease is one of middle and late age, and at that time people are prone to the divers hazards of advancing years. In some the leukemia will play little or no part in shortening life; in others the increased susceptibility to infection and lowered resistance to be expected from involvement of lymphoid tissue, even in the silent phase of the disease, may lead to a rapid death. It is therefore of the greatest importance to treat early and adequately any infection in these patients.

Summary

Nine cases of chronic lymphatic leukemia seen at an early stage of the disease are described. Three of these patients died shortly after the diagnosis of chronic lymphatic leukemia was established from causes unrelated to the leukemia, and autopsies were performed on two of these. The lymph nodes in both cases showed no histologic changes suggestive of leukemia, although well marked lymphocytic infiltration of the portal tracts of the livers and extensive lymphocytic infiltration of the bone marrows were present. In one of these two cases the spleen was not enlarged and showed no abnormal histologic changes apart from congestion. Lymph node biopsy was performed at a relatively early stage of the disease in three of the remaining cases; the nodes in these cases showed no leukemic changes, while a splenic biopsy performed in one of these also showed no leukemic changes.

It is concluded that lymph node biopsy is of no value in the diagnosis of early chronic lymphatic leukemia.

The leukocyte counts were below 45,000 per cubic millimeter in all but one of these cases, and from other early cases described in the literature it appears that the leukocyte count usually remains low for several years, and that anemia and thrombocytopenia are late manifestations of chronic lymphatic leukemia.

It is postulated that there are no signs or symptoms in the first stages of chronic lymphatic leukemia, and that this "silent" phase of the disease lasts many years. It is succeeded by a phase, also of many years' duration, in which there are signs of the disease but no symptoms. The classic picture of the disease, with anemia, gross splenomegaly, lymphadenopathy, thrombocytopenia and a very high white cell count, is considered to be only the terminal phase of a disease which usually runs a course lasting from 10 to 20 years.

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I wish to thank the members of the clinical staff of both the West London Hospital and the North Carolina Memorial Hospital for granting me permission to study their cases. I also wish to thank Dr. J. B. Wild and Dr. I. A. Goldberg, who in turn assisted me in the earlier part of this work.

SUMMARIO IN INTERLINGUA

Iste articulo describe le constatationes clinico-pathologic in nove casos de chronic leucemia lymphatic presentate a un stadio precoce del morbo. Tres de iste patientes moriva brevemente post que le diagnose de chronic leucemia lymphatic esseva establite. Le causas de mörte in iste tres casos non esseva relationate a leucemia. In duo casos autopsias esseva executate. Le nodos lymphatic del casos autopsiate monstrava nulle alterationes histologic de character suggestive de leucemia, sed ben marcate infiltrationes lymphocytic del medulla ossee esseva presente. In un de iste casos le splen non esseva allargate e non exhibiva ulle anormal alterationes histologic excepte le evidentia de congestion. Iste patiente habeva un associate carcinoma del esophago. In le altere patiente le autopsia revelava un carcinoma pulmonar non previemente suspicite. In tres del remanente casos, biopsias del nodos lymphatic esseva executate a un relativemente precoce stadio del morbo. In iste casos le nodos non monstrava ulle signo de alteration leucemic. Un biopsia splenic, executate pro un del patientes, etiam revelava nulle alteration leucemic. Es postulate le conclusion que le biopsia de nodos lymphatic es sin valor in le diagnose de precoce chronic leucemia lymphatic.

Le conto leucocytic esseva initialmente infra 45.000 per millimetro cubic in omne le casos con un exception. Ab iste observationes e ab le datos trovate in le litteratura, le conclusion es derivate que le conto leucocytic remane usualmente satis basse durante plure annos. Al tempore del prime discoperta de leucemia, nulle anemia esseva presente in sex del casos. In duo casos le anemia esseva insignificative. In le ultime caso del serie, anemia esseva le effecto de sanguination gastric; illo respondeva a therapia a ferro. Il pare per consequente que anemia es un manifestation tardive de chronic leucemia lymphatic. Thrombocytopenia es etiam un manifestation tardive.

Es postulate que il ha ni signos ni symptomas in le prime stadios de chronic leucemia lymphatic e que iste "silente" phase del morbo perdura multe annos. Le sequente phase, etiam de un duration de multe annos, es characterisate per le presentia

de signos e le absentia de symptomas del morbo. Le syndrome classic del morbo—con anemia, grossier splenomegalia, lymphadenopathia, thrombocytopenia, e un altissime conto leucocytic—es a considerar solmente como le phase terminal que curre usualmente durante un periodo de inter 10 e 20 annos. Le curso del morbo supra-delineate es le curso characteristic de casos non modificate per un therapia specificamente antileucemic. Solmente una del patientes in le presente serie de nove casos recipeva un tal therapia, e iste therapia esseva initiate durante le phase terminal.

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THE INTERRELATIONSHIPS BETWEEN ADDISON'S DISEASE AND ACTIVE TUBERCULOSIS: A REVIEW OF 125 CASES OF ADDISON'S DISEASE *

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THE difficulties of evaluating the effect of adrenal function on the course of an infection are well illustrated in the clinical problem presented by the spontaneous occurrence of active tuberculosis in the presence of Addison's disease. The purpose of the present report is to describe certain complexities in this relationship observed in a series of patients with adrenal insufficiency who have been followed over the past 20 years.

Endocrines and Infection: The effects of hormonal balances on infectious processes, and on tuberculosis in particular, have long been a field of interest. Studies on the influence of diabetes [1-4] and of pregnancy on tuberculosis,[5-15] however, have not resulted in any clearcut conclusions concerning the effects of endocrine fluctuations on the natural history of this infection. Studies on Cushing's syndrome, on the other hand, indicate that although tuberculosis is not a common complication, adrenal overactivity does predispose to serious pyogenic infections.[16]

Since the introduction of cortisone and pituitary adrenocorticotropic hormone (ACTH) into clinical medicine, first for the management of rheumatoid arthritis [17] and, more recently, for a variety of inflammatory and immuno-allergic states,[18] a new dimension has been added to the traditional formula for the host-parasite relationship. Attention to the details of the endocrine effects, however, shows that they are contributing but not autonomous factors.

Effect of Increased Adrenocortical Activity on Infection: Following the introduction of cortisone and ACTH, there appeared numerous observations of their rôle in the natural history of many infectious diseases.[19] Excessive doses of adrenal steroids were shown to enhance the morbidity and mortality of experimental tuberculosis in animals.[20-43] The rôle of natural and acquired resistance, however, was not controlled in these studies. Where these factors were taken into consideration, it was found that smaller doses of

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cortisone offer certain aspects of protection to inbred strains of highly susceptible rabbits given minimal infecting doses of tubercle bacilli.[26]

These earlier laboratory observations were soon followed by clinical observations on patients with latent or active tuberculosis in whom cortisone and ACTH had deleterious effects on the course of the disease.[44-49] More recent reports suggest that, in combination with antibiotic therapy, cortisone may be an adjunct to the treatment of tuberculous meningitis,[50] and may even have a rôle in the therapy of pulmonary tuberculosis.[51, 52] Neither these scattered case reports nor the various animal experiments, which were designed to study a single facet of the host-parasite relationship, justifies any clearcut conclusion regarding human tuberculosis and steroid therapy.

Rôle of Adrenal Insufficiency on Infection: Information about the rôle of adrenal insufficiency on the course of tuberculosis is even less complete than that about the effect of increased adrenocortical activity on infections in normal subjects. There has been a clinical impression, substantiated by sporadic case reports,[53-56] that adrenal insufficiency increases resistance to reactivation or progression of chronic tuberculosis.[57-59] Data have also been presented to show that active infections frequently impose greater difficulties on the management of adrenal insufficiency.[60] A further consideration of this relationship forms the body of the study which follows.

Materials and Methods

The records of 125 patients with an unequivocal diagnosis of adrenal insufficiency were reviewed. Both the clinical nature of this study and the changing methods of medical observation and treatment over the long period during which individuals were followed have complicated this presentation. To simplify exposition, much of the data has been condensed into tables. In the interests of brevity, these tables and other clinical results are combined with the discussion which follows this section.

Diagnostic criteria for the inclusion of patients in this study were briefly as follows:[59]

(a) *History:* Most of the patients gave a history of malaise, ease of fatigue, gastrointestinal disturbances, anorexia, weight loss and other nonspecific symptoms.

(b) *Physical examination:* Hypotension was almost universal in these patients before treatment. Except very early in the disease, most patients had aberrations in pigmentation of skin and mucous membranes.

(c) *Laboratory findings:* Anemia and a relative lymphocytosis were common findings. Electrolyte disturbances, with hyponatremia, azotemia, hypochloremia and hyperkalemia, were observed in untreated individuals in whom the disease was of long duration, or in whom crisis was imminent. Special tests of adrenocortical function were employed in all these individuals. Tests prior to 1947 included a study of the ability to handle an acute water

load (Robinson-Power-Kepler test), the inability of the body to conserve sodium or chloride under conditions of deprivation (Cutler-Powers-Wilder test), and an increased susceptibility to hypoglycemia following prolonged fasting or insulin administration. After 1947, all individuals were tested with ACTH. The indices of activity commonly followed were a lack of fall in the circulating eosinophils and a lack of rise in the urinary excretion of steroids.

Additional studies evaluated in this report were regularly carried out on most individuals. These consisted of routine blood analyses, including erythrocyte sedimentation rates (Wintrobe method), roentgenograms of the chest and abdomen, skin testing for delayed reactivity to tuberculin, and efforts to isolate *Mycobacterium tuberculosis* (from urine, sputum, gastric aspiration or pathologic fluids) by morphologic, cultural and/or animal inoculation technics.

Observations and Discussion

General Interrelationships Between Tuberculosis and Addison's Disease: The clinical records and pathology reports of these individuals with Addison's disease were evaluated in an effort to ascertain the validity of clinical criteria in determining the probable etiology of their adrenal insufficiency. In the entire group no previous definite history of tuberculosis could be elicited from 94 (75.2%) of the patients (table 1). In 59 of these 94 patients, studies were carried out in an attempt to ascertain whether clinically inapparent tuberculosis might have been responsible for their adrenal insufficiency.

"Definitive" studies were standard tuberculin skin tests and/or cultures for *M. tuberculosis.* The tuberculin test was considered "positive" if at 48 hours the diameters of the area of induration exceeded 5 by 5 mm., or if they were merely recorded as positive. For tabulation, first-strength purified protein derivative (PPD-S) and 1:10,000 Old Tuberculin (OT) were considered equivalent, as were second strength PPD-S and 1:1000 OT.

These findings were further correlated with other clinical and laboratory features frequently considered in the evaluation of these patients, including a family history of tuberculosis, x-ray findings suggestive of pulmonary tuberculosis, and adrenal calcification.

Table 1

125 Cases of Addison's Disease

No clinical history of tuberculosis	94	(75.2%)
* Definitive studies for tuberculosis carried out	59	
No definitive studies for tuberculosis carried out	35	
Clinical history of tuberculosis	31	(24.8%)
Definitive studies for tuberculosis carried out	30	
No definitive studies for tuberculosis carried out	1	

* Definitive studies were either tuberculin test and/or cultures of sputum, gastric washings and/or urine for *M. tuberculosis.*

TABLE 2

Addison's Disease with No History of Tuberculosis

Studies and Results	Number of Cases	F. H.* Tbc.	"Old" Tbc.	Adrenal Uni.	Calc. Bilat.
Definitive studies for tuberculosis	59	5	20	2	6
Tuberculin test	32				
Positive	17	1	6	0	3
Diluted 1st strength	2	0	0	0	0
1st strength	8	0	4	0	2
2nd strength	7	1	2	0	1
Negative	15	0	3	0	1
1st strength	5	0	3	0	1
2nd strength	10	0	0	0	0
Not done	27	4	11	2	2
Cultures	34				
Positive	0				
Negative	34				
No definitive studies for tuberculosis	35	6	18	0	0

* F. H., family history.

A family history of tuberculosis was considered to be present if (a) either the parents or siblings had tuberculosis, or (b) other relatives had tuberculosis, and specific mention of frequent contact was made in the record. A family history of tuberculosis bore little relationship to the presence of tuberculin sensitivity (table 2).

Roentgenographic changes compatible with previous tuberculosis ("old tuberculosis") correlated more closely with tuberculin reactivity, even though differences existed in both positive and negative reactors. The term "old tuberculosis" is used here to describe roentgenographic findings reported as "inactive or old pulmonary disease, probably of tuberculous origin," "a primary complex of tuberculosis, consisting of both a calcified parenchymal lesion and calcified hilar lymph nodes," or "marked thickening of the apical pleura" (noted in three persons). Adrenal calcification, uncommon in this group, was present in eight persons (13.6%).

The poor correlation between the various features which might have

TABLE 3

Interrelationships between Evidences of Tuberculosis

Evidence of Tuberculosis	Number of Cases	F. H.* Tbc.	"Old" Tbc.	Ad. Calc.†
Family history	5	—	2	1
"Old" tuberculosis	11	2	—	3
Adrenal calcification	8	1	3	—

* F. H., family history.
† Ad. Calc., adrenal calcification.

TABLE 4

Addison's Disease with History of Tuberculosis

Studies and Results	Number of Cases	F. H.* Tbc.	"Old" Tbc.	Ad. Uni.	Calc.† Bilat.
Active tuberculosis plus Addison's (either before or after)	31	10	—	6	5
Active tuberculosis post-Addison's	18	6	—	2	3
Active tuberculosis pre-Addison's	13	4		4	2

* F. H., family history.
† Ad. Calc., adrenal calcification. Uni., unilateral. Bilat., bilateral.

suggested tuberculosis was further borne out in a comparison of the relations between family history, "old tuberculosis," and adrenal calcification (table 3).

The problems encountered in attempting to evaluate the etiology of adrenal insufficiency on the basis of clinical history or laboratory findings are well demonstrated by this group of 94 patients with no personal history of tuberculosis. Reactivity to tuberculin seems to be one of the most useful technics, though Rowntree and Snell mentioned that, in some cases of adrenal tuberculosis, sensitiveness to tuberculin was absent.[57] In the evaluation of patients with Addison's disease, the tuberculin-negative individual probably does not have tuberculosis of the adrenals. On the other hand, the tuberculin-positive person may or may not have adrenal tuberculosis.

A history of clinical tuberculosis was elicited from 31 individuals (24.8%) (table 4). This group includes those persons whose active tuberculosis antedated the onset of adrenal insufficiency, as well as those who had active tuberculosis at some time in the presence of established and diagnosed adrenal insufficiency. In this group, adrenal calcification was more common (35.5%) than in the tuberculin-negative group (6.7%). A history of familial exposure to tuberculosis was also common (32.3%) in those with active tuberculosis.

TABLE 5

Postmortem Findings on Patients with No History of Tuberculosis

Patient	Definitive Studies for Tuberculosis		Cause of Adrenal Insufficiency		Other Tbc. at Post Mortem	F. H.* Tbc.	"Old" Tbc.	Ad. Calc.†
	Tuberculin Test	Culture	Atrophy	Tbc				
L. C. 69523	Neg.		x		None	0	0	0
J. D. 65745	Neg.		x		None	0	0	0
E. D. 64632	—	Neg.	x		None	0	0	0
S. W. 64564	—	Neg.		x	None	0	0	0
G. B. 64195	—	—		x	Splenic	0	0	0
J. L. 66509	—	—	x		Pulmonary	+	+	0

* F. H., family history.
† Ad. Calc., adrenal calcification.

The available pathologic reports in this series confirmed antemortem diagnoses and substantiated the clinical criteria used in the etiologic diagnosis of those patients not studied at autopsy. These reports also clarified the rôle of fibrocaseous tuberculosis as a cause of adrenal insufficiency in these patients. Postmortem studies were done on six of the 94 persons who gave no history of tuberculosis (table 5). The last patient in the table (J. L., PBBH 66509) unfortunately was not thoroughly studied from a clinical standpoint. He had healed bilateral apical pulmonary tuberculosis and idiopathic atrophy of the adrenals.

Postmortem studies were performed on six patients from the group with clinically active tuberculosis in the presence of adrenal insufficiency (table 6). In all except one patient (W. T., PBBH 68600), the studies revealed active

TABLE 6

Postmortem Findings on Patients with Active Tuberculosis

Patient	Type of Clinically Active Disease	Cause of Adrenal Insufficiency		Sites of Tbc.	Sites of Active Disease at Autopsy
		Atrophy	Tbc.		
M. S. 57425	Cervical lympha-denitis		x	Abd. lymph nodes, liver, spleen, adrenal, cerv. nodes	Abd. nodes, cerv. nodes, liver
E. M. 46135	Pulmonary		x	Adrenal, lungs, renal, abd. nodes	Abd. nodes, lungs
R. M. 43784	Pulm. and meningitis		x	Adrenal, lungs, cerebellum, meninges, pancreas, liver	Tuberculoma of cerebellum
W. T. 68600	Pulmonary	x		Lungs (inactive)	None
H. G. 70616	Miliary		x	Lungs, spleen, liver, kidney, brain, fallopian tubes, abd. nodes, adrenal	All sites
S. M. 56808	Pulmonary		x	Adrenal, kidney, liver, abd. nodes, lung	All sites except lung

tuberculosis in the adrenals and multiple foci elsewhere. One additional patient (P. G., PBBH 50545), who had had active pulmonary and vertebral tuberculosis 18 years prior to the onset of symptoms of adrenal insufficiency, was studied. At postmortem examination caseous lesions were found in both adrenals. There were bilateral psoas abscesses and old involvement of the lungs, vertebrae and spleen. Since all active tuberculosis had antedated the adrenal insufficiency, this patient is not included in either table 5 or table 6.

In all, 13 patients were studied post mortem (tables 5 and 6). Six had had active tuberculosis in the presence of adrenal insufficiency. Five still had active tuberculosis at the time of death. Of these five, all had tuberculosis of the adrenals as well as active lesions elsewhere. The remain-

TABLE 7

Relationship between the Primary Diagnosis of Adrenal Insufficiency and Tuberculosis

Condition Diagnosed Earliest	Number of Cases	Time Interval in Years	
		Range	(Mean)
Adrenal insufficiency	5	1–4	(2)
Tuberculosis	6	11–22	(15)
Simultaneous*	7		

* Difference of less than one year.

ing eight had either inactive tuberculosis at the time of death or no evidence of tuberculosis. Three of these eight had had tuberculosis of the adrenals. The remaining five had idiopathic atrophy of the adrenals.

In Ustvedt's series, adrenal tuberculosis was thought to be a very late residual of primary tuberculosis.[61] In the present study the duration of time between the onset of clinical symptoms of tuberculosis and adrenal insufficiency (table 7) could not be arranged according to such a timetable because most patients did not have symptoms suggestive of tuberculosis. Furthermore, in at least two instances tuberculosis was present elsewhere in persons with idiopathic adrenal atrophy (J. L., PBBH 66509, and W. T., PBBH 68600).

Specific Interrelationships Between Active Tuberculosis and Established Adrenal Insufficiency: A total of 31 of the 125 patients had had active tuberculosis at one time or another during their lifetimes. As noted in table 4, 18 of the 125 persons (14.4%) had active clinical tuberculosis at a time when adrenal insufficiency was present. In five of these 18 patients, reactivations or spreads of the tuberculosis occurred more than one year after

TABLE 8

Type of Clinically Active Tuberculosis

Single Active Focus		Multiple Active Foci	
Location	Number of Cases	Location	Number of Cases
Pulmonary	8* (5)†	Pulm. and G.U.	5* (3)†
Genitourinary	4 (1)	Pulm., G.U. and osteo.	3 (3)
Peritonitis	2 (2)	Pulm. and osteo.	2
Osteomyelitis	1	Pulm. and tenosynovitis	2 (1)
Lymphadenitis	1 (1)	Pulm. and cerebellar	1 (1)
		Pulm. and miliary	1 (1)
		Osteo. and miliary	1
Total	16 (9)		15 (9)

* Total number of cases occurring either before or after onset of adrenal insufficiency.
† Number in parentheses refers to the number of cases with clinically active tuberculosis in the presence of adrenal insufficiency.

adrenal insufficiency was established (table 7). In the rest, clinical evidence of active tuberculosis either antedated or appeared soon after the onset of adrenal insufficiency.

In 22 of these 31 individuals there was pulmonary tuberculosis, occurring either as the only focus of activity or in combination with other sites (table 8). The sites of tuberculous activity in the presence of adrenal insufficiency were similar in incidence and location to those in the entire group with a history of tuberculosis.

Effect of Tuberculosis and Antituberculous Therapy on Addison's Disease and on Requirements for Hormonal Replacement Therapy: To some extent, the effect of active tuberculosis on adrenal insufficiency could be judged by the requirement of hormone necessary to maintain homeostasis (table 9). Basic hormone requirements were estimated from the dosage

TABLE 9

Effect of Active Tuberculosis upon Hormone Requirements

Type of Tuberculosis (No. Cases)	Hormone Rx		Dosage Level	
	Type	No. Cases	Normal	Increased
Pulmonary (9)	DOCA,	7	3	4
	Cortisone and DCTMA	2	2	0
Genitourinary (4)	DOCA,	3	2	1
	Cortisone	1	1	0
Peritonitis (2)	DOCA,	1	0	1
	Cortisone	1	0	1
Osteomyelitis (1)	DOCA	1	0	1
Lymphadenitis (1)	DOCA	1	0	1
Total (17)	DOCA	13	5	8
	Cortisone	4	3	1

at a time when the tuberculosis was inactive, either before activation, after quiescence, or at both times, where the course of the diseases permitted.

Those individuals who were maintained on salt-retaining hormone, on whole adrenal cortical extract, or on lipo-adrenal extract, often required significantly more hormone during the period of active tuberculosis (eight of 13 individuals) (table 9). For example, one person (C. F., PBBH 67740) was too weak to shave even when the number of desoxycorticosterone (DOCA) pellets was increased from four to eight (125.0 mg. each), and supplements of Percorten (0.5 ml. containing 2.5 mg. DOCA) were given daily. In other patients, not only were larger replacement doses needed, but, in addition, lability in requirements often complicated therapy. Implantation of a suboptimal number of DOCA pellets and the use of a variable daily supplement of injectable compounds were usually recommended.[60]

Part of the difficulty in regulating DOCA dosage in these patients may have been the result of the chloride-losing tendency which tuberculosis without adrenal insufficiency is known to produce.[62]

Four persons were treated with cortisone and the long-acting, injectable trimethyl ester of DOCA (DCTMA).[63] In one of these (D. R., PBBH 9B240), an increased cortisone dosage was needed to avoid undue fatigue (12.5 to 25 mg. daily). Replacement therapy with cortisone in these four persons alleviated much of their previous symptomatology.

Antituberculous drugs were given to six persons. Three patients received dihydrostreptomycin (DHSM) and three streptomycin (SM) in combination with either para-aminosalicylic acid (PAS) or isonicotinic acid hydrazide (INH) (table 10). These drugs seemed to have little demonstrable effect on the adrenal insufficiency. One individual (D. R., PBBH 9B240), however, complained of increased malaise and anorexia while receiving 12.0 gm. of PAS daily. When he was changed to isonicotinic acid hydrazide (INH) he experienced no further trouble. This was considered to be a possible indication for increased DOCA need. It may well have been a toxic manifestation of PAS. Three of six persons developed eighth-nerve toxicity on relatively small amounts of either SM or DHSM. This finding suggests that patients with Addison's disease may be more prone to develop auditory nerve toxic manifestations with these drugs than are patients with uncomplicated tuberculosis.

In Male's study, a group of 19 patients was found to have adrenal insufficiency while in a tuberculosis sanatorium.[64] They were not treated with

TABLE 10

Drug Therapy in Addisonian's with Active Tuberculosis

Patient	Type of Tuberculosis	Drug*	Dosage (gm./unit time)	Duration	Toxicity
H. J. 5A457	Pulm.	DHSM	2.0 q.d.	13 days	Hearing loss
J. F. 6A226	GU	DHSM	2.0 q.d. 1.0 q.d.	30 days 90 days	Hearing loss
H. S. 6A463	Peritonitis	DHSM	1.0 q.d. 2.0 q.d.	28 days 9 days	None
H. M. 5A487	Pulm.	SM PAS	1.0 twice weekly 12.0 q.d.	12 mos. 12 mos.	None
S. P. 6A657	GU	SM PAS	1.5 q.d. 6.0 q.d.	10 days 6 days	Vertigo
D. R. 9B240	Peritonitis	SM INH	1.0 twice weekly 0.2 q.d.	90 days 90 days	None

* DHSM, dihydrostreptomycin.
SM, streptomycin.
PAS, para-aminosalicylic acid.
INH, isonicotinic acid hydrazide.

TABLE 11
Course of Active Tuberculosis in Addison's Disease

Type of Active Tuberculosis (No. Episodes)	Hormone Rx		Anti-Tbc. Rx		Course of Tbc.		
	Type	No. Episodes	Type	No. Episodes	Fatal	Mod. Spread	Regressed
Pulmonary (12)	None	3	None	3	3		
	DOCA	7	None	2			2
			Drug*	1		1	
			Rest	4	2	1	1
	Cortisone DCTMA	2	None	1		1	
			Drug	1			1
Genitourinary (4)	DOCA	3	None	1		1	
			Drug	1			1
			Nephrect.	1			1
	Cortisone	1	Drug and nephrect.	1			1
Peritonitis (2)	DOCA	1	Drug	1			1
	Cortisone	1	Drug	1			1
Osteomyelitis (1)	DOCA	1	X-ray	1			1
Miliary (1)	None	1	None	1	1		
Lymphadenitis (1)	DOCA	1	X-ray	1	1		
Total (21)					7	4	10

* Drugs consisted of streptomycin, dihydrostreptomycin and/or isonicotinic acid hydrazide; also, rest was usually combined with drug therapy.

DOCA pellets because of the lability of hormonal requirement. Ten of these patients were considered to have enough symptoms to warrant replacement therapy. The average survival in the treated cases was 8.0 months; in the untreated cases, 4.6 months. Fourteen of these 19 patients died in adrenal crisis. Even with replacement therapy, Male found that the prognosis of active tuberculosis in the presence of Addison's disease was poor. With DOCA therapy alone, death in his patients was the result of adrenal crisis rather than of progressive tuberculosis.

The prognosis in a comparable number of patients in our study with active tuberculosis and Addison's disease was somewhat better than that reported by Male. Three persons of the 14 who received hormonal replacement therapy died, each in adrenal crisis (table 11). Recent dissemination of tuberculosis was found at autopsy in two of these individuals.

The effects of active tuberculosis and adrenal insufficiency can be summarized by saying that active tuberculosis in the presence of adrenal insuf-

ficiency may increase the requirement for salt-retaining hormone (DOCA) and, to a lesser degree, may increase the patient's daily cortisone requirement. Active tuberculosis may also increase the lability of daily DOCA requirements. Specific antituberculosis therapy does not alter significantly the management of hormonal control except where surgery is an adjunct to treatment. Under these circumstances, hormonal management during surgery should be the same as in other persons with adrenal insufficiency undergoing operations.

Effect of Addison's Disease and Hormonal Replacement on Active Tuberculosis and Antituberculous Therapy: Adrenal insufficiency has been thought to confer a certain degree of resistance to active tuberculosis on the host. This view has come from clinical observations [57-59] on individual cases and from epidemiologic data on the incidence of active tuberculosis in patients with Addison's disease.[57] These conclusions bear reëxamination. In one study, 21 of 31 cases had active tuberculosis in the presence of adrenal insufficiency.[57] In another study, six of 22 cases had active disease outside of the adrenals.[65] Guttman noted that the mean survival time in 35 cases with "active and marked tuberculosis" and Addison's disease was 12.04 ± 1.33 months, while that for 50 cases with "minimal or healed" disease was 14.40 ± 1.60 months.[66] An objection can be raised to the acceptance of these data at face value. It includes minimal though active disease with healed tuberculosis. This objection is supported by further data from Guttman's paper. He found that the mean survival time for adrenal insufficiency due to tuberculosis is 13.31 months, as compared to 34.02 months for idiopathic adrenal atrophy. This difference is highly significant. Other workers have taken the contrary view—that the prognosis for the two diseases in the same individual [64, 67] is exceedingly poor.

In our series, as noted previously, 18 of 31 individuals with a history of previous tuberculosis had coincident activity of both diseases (table 4). In five of the 18 cases, adrenal insufficiency antedated the acquisition of clinical tuberculosis (table 7). Among the 18 patients there were 21 distinct episodes of activation of tuberculosis (table 11).

Four of these 18 persons received no hormonal therapy. The course of their disease was of short duration, and no conclusions regarding the relative rôle of either adrenal insufficiency or tuberculosis can be drawn.

The remaining 14 patients all received hormonal replacement therapy. Three of these individuals died while both diseases were uncontrolled. All three had terminal signs of adrenal crisis, while two of the three were found to have had a recent hematogenous spread (M. S., PBBH 57425, and S. M., PBBH 56808). In eight of the 14 patients, 10 foci of infection became quiescent under hormonal and, in some instances (five persons), under antituberculous therapy. The remaining three persons in the group had four distinct episodes of active pulmonary tuberculosis. During observation their disease was characterized by recurrent periods of reactivation and

by a moderate progression. One patient also developed clinical tuberculosis in his remaining kidney two years after previous nephrectomy for tuberculosis.

There is little evidence from these case studies to support the statement that the presence of adrenal insufficiency raises the threshold of resistance to active tuberculosis. On the contrary, there is evidence that the presence of the two diseases together decreases the likelihood of survival over that for either condition occurring by itself.

Of four patients to whom cortisone was administered in doses of 12.5 to 25.0 mg. daily, only one developed reactivation with a moderate spread of pulmonary tuberculosis (J. F., PBBH 6A226). An additional three persons were changed to cortisone from DOCA and ACE shortly after their tuberculosis was under control. They have shown no evidence of reactivation.

No conclusions regarding the relative effectiveness of antituberculous therapy in this small group of patients are justified. On general principles, however, it does not seem wise either to allow these patients relatively normal activity or to refrain from the use of available antituberculous drugs in their clinical management on the ground that they handle their tuberculosis effectively.

Browne and co-workers have recently treated five patients who had concomitant Addison's disease and active tuberculosis. They used cortisone, supplementary salt, streptomycin and PAS.[88] Their patients did well on the usual daily doses of cortisone (12.5 mg. to 37.5 mg.), with no evidence of further spread of their pulmonary tuberculosis. In fact, if anything, these observers felt that clearing of the chest lesions was more rapid than is usually observed when cortisone is not used. This improvement was maintained for from one to three and one-half years after cessation of antituberculous therapy.

In the presence of adrenal insufficiency, active tuberculosis shows the same tendencies toward chronicity and relapses which characterize its course in persons without Addison's disease. Hormonal replacement therapy is essential for these patients. There is no evidence that the doses of cortisone required to maintain hormonal balance predispose these patients to spread of their tuberculosis. Antituberculous therapy should be based on the same medical and surgical principles applied to individuals who do not have coincident adrenal insufficiency.

Clinical and Laboratory Features of Active Tuberculosis in the Presence of Addison's Disease: The constitutional symptoms and laboratory findings of both tuberculosis and adrenal insufficiency are often nondescript. Clinical features in the patient with adrenal insufficiency which seem to be altered following activation of tuberculosis are given in table 12. For the purpose of "controls," patients with negative tuberculin skin tests were designated as "normals." Although small, this group, rather than the larger group,

was used as a "control" because the latter may have contained examples of undetected active tuberculosis. Patients with Addison's disease and coincident active tuberculosis usually have (1) more severe symptoms, (2) tachycardia, (3) a low grade fever with increased diurnal fluctuation, (4) an elevated sedimentation rate, and (5) leukocytosis with a relative lymphopenia. The development of active genitourinary tuberculosis does not tend to augment the symptoms and signs in patients with Addison's disease.

TABLE 12

Clinical and Laboratory Features of Tuberculosis in Addison's Disease*

Clinical Condition	Number Cases	Increased Treatment Requirements of Addison's			Pulse Rate			Unexplained Fever (>100)	
		Yes	No	?	<80	80–100	>100	Yes	No
Tuberculin neg.	14	—	—	—	11	3	0	0	14
Active Tbc.	18	9	5	4	3	6	9	10	8
Pulm.	9	4	2	3	2	2	5	5	4
GU	4	2	2	0	1	3	0	1	3
Others	5	3	1	1	0	1	4	4	1

Clinical Condition	Number Cases	Sed. Rate			WBC (1000's)			Lymphocytosis		
		<20	20–40	>40	<5	5–10	>10	<40	40–60	>60
Tuberculin neg.	14	5	1	0	4	10	0	4	8	2
Active Tbc.	18	2	7	4	2	13	3	13	5	0
Pulm.	9	1	3	2	0	7	2	7	2	0
GU	4	1	1	1	1	3	0	2	2	0
Others	5	0	3	1	1	3	1	4	1	0

* In instances where observations total less than total number of cases, the particular observation was not made.

SUMMARY AND CONCLUSIONS

1. The interrelationships between adrenal insufficiency and active tuberculosis have been studied in a series of patients with Addison's disease. Eighteen patients are reported who had active clinical tuberculosis at a time when adrenal insufficiency was present.

2. Clinical and laboratory methods for establishing the cause of adrenal insufficiency have been found to have many limitations. The most useful of these findings are adrenal calcification, which is suggestive of a tuberculous etiology, and nonreactivity to tuberculin, which is suggestive of idiopathic adrenal atrophy.

3. Hormonal replacement therapy for adrenal insufficiency is essential for the management of Addison's disease with or without active tuberculosis. Doses of cortisone which are required to maintain hormonal balance did not cause a spread of tuberculosis in the patients of this study.

4. Active tuberculosis in the presence of adrenal insufficiency shows tendencies toward chronicity and relapse similar to those which characterize tuberculosis in persons without Addison's disease. Antituberculous therapy should be based on the same medical and surgical principles which are applicable to individuals who do not have concomitant adrenal insufficiency.

5. In a patient with known adrenal insufficiency, the appearance of increased symptoms, increased hormonal requirements, tachycardia, fever, leukocytosis with a relative lymphopenia, and an elevated erythrocyte sedimentation rate should suggest the presence of either active tuberculosis or some similar chronic infection.

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SUMMARIO IN INTERLINGUA

Le relationes inter insufficientia adrenal e tuberculose active esseva studiate in un serie de 125 patientes con morbo de Addison. Es reportate 18 patientes qui habeva active tuberculose clinic a un tempore quando insufficientia adrenal esseva presente. Esseva trovate que multe limitationes restringe le methodos clinic e laboratorial pro le determination del causa de insufficientia adrenal. Le plus utile factores es calcification adrenal que suggere un etiologia tuberculotic e nonreactivitate a tuberculina que suggere atrophia adrenal idiopathic.

Un hormonal therapia substitutive pro insufficientia adrenal es essential in le manipulation de morbo de Addison sin o con tuberculose active. Le doses de cortisona requirite pro mantener le balancia hormonal non extendeva le tuberculose in le patientes del presente studio. Tuberculose active in le presentia de insufficientia adrenal exhibi tendentias de chronicitate e recidiva in formas simile a lo que characterisa tubercuose in personas sin morbo de Addison. Le therapia antituberculotic deberea esser basate super le mesme principios medical e chirurgic que es applicabile a individuous qui non ha concomitante insufficientia adrenal.

In un patiente in qui insufficientia adrenal es establite, le presentia de tuberculose active o de un altere simile infection chronic es suggerite per le constatation de augmentate symptomas, de augmentos del requirimentos hormonal, de tachycardia, de febre, de leucocytosis con lymphopenia relative, e de un accelerate sedimentation erythrocytic.

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ADRENAL INFLUENCES ON THE STOMACH: PEPTIC ULCER IN ADDISON'S DISEASE DURING ADRENAL STEROID THERAPY *

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A RELATIONSHIP between the adrenal gland and the stomach has been demonstrated by an increased gastric acid and pepsin secretion during adrenal stimulation. The adrenal gland has been implicated in the pathogenesis of peptic ulcer disease by the development or reactivation of peptic ulcer during the administration of ACTH or the adrenal steroids.[1-5] Conversely, patients with adrenal hypofunction (Addison's disease) characteristically present a decrease in gastric acidity and an unusually low incidence of chronic peptic ulcer.

It has been postulated that emotional duress and other alarm stimuli may produce acute and chronic peptic ulcer in man by a hypothalamic-pituitary-adrenal pathway to the stomach, independent of neurogenic transmission.[2, 3, 4]

The adrenal-gastric relationship may be considered to be on a "permissive" conditioned basis, in accord with the recent hypotheses of Selye [6] and Ingle.[7] Under normal circumstances the stomach enjoys a semi-autonomous rôle relative to the adrenal cortex, requiring the presence of normal adrenocortical function for acid-peptic activity. During conditions of stress, however, the stomach is more directly under adrenocortical control.[5]

The parallelism between gastric and adrenal function will be demonstrated in this report by a decreased peptic activity in patients with adrenal insufficiency, and by an increased gastric secretion in patients with pituitary and adrenal overactivity (Cushing's disease).

The significance of the adrenal gland in peptic ulcer disease is emphasized in this presentation by the observation of gastric or duodenal ulcers developing in patients with Addison's disease during glucocorticoid replacement therapy, accompanied by an increase in gastric secretion.

The rarity of chronic peptic ulcer in patients with Addison's disease has been reported by various investigators. Maranon [9] found no peptic ulcers in 25 postmortem examinations of addisonian patients, although he mentions

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three clinical cases of peptic ulcer in 160 patients. There is some question whether these three ulcers were true chronic peptic ulcers. A similar absence of peptic ulcer was observed by Schmidt [10] in 25 proved addisonians. Bastenie [11] did not find a single ulcer among 58 patients, 20 of whom were examined at autopsy.

In a review of 120 cases of Addison's disease by Jarvis et al.,[12] only 24 patients were studied by roentgenologic examination, because of digestive complaints. Deformity of the duodenal bulb without a demonstrable crater was observed in two instances, in both of whom an ulcer history preceded the development of the adrenal insufficiency.

The infrequency of chronic peptic ulcer in Addison's disease appears to be associated with a decreased secretion of hydrochloric acid. Grawitz [13] was the first to note the achylia in this disease, an observation which has been confirmed repeatedly by many investigators. Rowntree and Snell [14] observed achlorhydria in 53% of the patients studied, with a considerable reduction in free acid in all but two of the remaining cases. More recently other investigators, notably Soffer [15] in 1948 and Sorkin [16] in 1949, observed achlorhydria in approximately 50% of patients with Addison's disease. Feyrter and Klima [17] found a similar reduction in free acid in their series of Addison's disease patients, a majority of whom demonstrated histamine anacidity. Maranon [9] noted a decrease or suppression of hydrochloric acid secretion in more than one-half of the cases. Recently Stempien [18] reported a case of untreated Addison's disease exhibiting a markedly diminished acid response following histamine stimulation.

Animal experiments provide further evidence of the significant rôle of the adrenal cortex in maintaining normal gastric secretory activity. Tuerkischer and Wertheimer [19] noted a marked decrease in gastric secretion after bilateral adrenalectomy in rats, but observed no effect after removal of the adrenal medulla alone. The fall in secretion could be reverted to normal by the administration of adrenocortical extract but not with desoxycorticosterone acetate or normal saline. Madden and Ramsburg [20] demonstrated a reduction in the volume of gastric secretion in pylorus-ligated rats following adrenalectomy. The administration of saline and desoxycorticosterone acetate partially restored the volume of gastric secretion. Recently Welbourn and Code [21] also reported that adrenalectomy of the pylorus-ligated rat produced a significant decrease in acid secretion, which was restored to normal with cortisone. Similarly, Haroutunian and Segal [22] noted a fall in gastric volume in adrenalectomized Shay rats with protection against ulceration in these experimental animals. Porter et al.[23] found that the delayed acid response produced by electrical stimulation of the posterior hypothalamus in monkeys could be abolished by bilateral adrenalectomy.

The histologic examination of the majority of stomachs of Addison's disease patients with achylia demonstrated atrophy, interstitial inflammation and replacement of the fundic glandular cells by mucoid cells with almost

complete disappearance of the parietal cells.[17] In adrenalectomized rats Baker and Bridgman [24] found, within a three week period, reduction in size of the cellular elements lining the gastric pits and tubules, the mucoid chief cells and zymogenic cells showing the most involution.

In the studies to be described, pepsinogen excretion in the urine (uropepsin) was used as a quantitative test of gastric secretory function. Previous studies [25] would indicate that it is an accurate reflection of gastric pepsin output and represents a constant fraction of the total pepsinogen production by the peptic chief cells, approximating 1%.

Method

Daily 24 hour uropepsin excretions were determined by our modification of the method described by Bucher,[26] as previously reported.[27]

Twenty-four hour urine specimens were collected and refrigerated immediately. An aliquot of 20 c.c. of urine was adjusted to pH 1.5 and made up to 25 c.c. with distilled water as described by Mirsky.[28] One cubic centimeter of this acidified urine was incubated with 5 c.c. of 2.5% denatured acidified hemoglobin substrate at 37° C. for 30 minutes. Ten cubic centimeters of trichloracetic acid were added to stop the reaction, and the concentration of tyrosine-like substances in 5 c.c. of the filtrate was determined by the Folin-Ciocalteu procedure with the use of a photoelectric colorimeter.

To correct for chromogenic substances present in the urine and substrate prior to proteolysis, 1 c.c. of the acidified diluted urine and 5 c.c. of hemoglobin substrate were added directly to trichloracetic acid and the color was determined as described. The difference in colorimeter readings between the incubated and unincubated specimens indicated the production of tyrosine-like substances resulting from proteolysis. Peptic units were then calculated with the aid of a standard curve.

The unit of activity of uropepsin was defined arbitrarily in this study as that amount which, during 30 minutes of incubation at 37° C. in the standard assay, released 0.04 mg. of tyrosine-like substances. Results were expressed as units per cubic centimeter of undiluted urine or units excreted in 24 hours.

The 24 hour urinary 17-hydroxycorticoids were determined by the method of Reddy, Jenkins and Thorn,[29] and the urinary 17-ketosteroids by a modification of the method of Drekter et al.,[30] whereby the colorimetry was performed as in the procedure of Holtorff and Koch.[31]

Results

Uropepsin and Adrenal Steroid Excretion

"Normal" Subjects and Peptic Ulcer Patients: The uropepsin excretion of 265 normal subjects and patients without demonstrable gastrointestinal disease ranged from 1,200 units to 8,000 units, with a mean of 3,670 units

TABLE 1

Mean Uropepsin Excretion in Normal Subjects and in Peptic Ulcer Patients

	Number of Cases	Uropepsin Excretion (units/24 hours)
Normal	265	3670 (S.E. ± 159)
Duodenal ulcer	205	8470 (S.E. ± 275)
Gastric ulcer	90	5760 (S.E. ± 414)

in 24 hours and a standard error of ± 159 units. In 205 patients with active duodenal ulcer the mean excretion was elevated to 8,470 units (S.E. ± 275), compared to an output of 5,760 units (S.E. ± 414) observed in 90 patients with gastric ulcer (table 1).

Addison's Disease: Patients with Addison's disease demonstrate a marked diminution in uropepsin excretion. The mean 24 hour output of 12 patients receiving desoxycorticosterone alone, without supplementary glucocorticoid therapy, was 540 units per 24 hours (S.E. ± 109). This represents an 85% reduction from the normal mean excretion and parallels the decrease in urinary corticoid excretion. The mean 17-ketosteroid excretion was 3.7 mg. per 24 hours, reflecting a 75% reduction in output. A similar reduction in 17-hydroxycorticoids was seen (tables 2 and 3).

Effect of Glucocorticoid Therapy: With replacement glucocorticoid therapy, the uropepsin excretion of 11 patients with Addison's disease returned to normal levels or above, depending upon the replacement dosage. The mean for 11 cases was 4,080 units, which is within the higher range of normal (table 2). The Addison's disease patient appears to demonstrate a relatively exaggerated uropepsin response percentagewise to small daily doses (12.5 to 50 mg.) of cortisone compared to normal individuals given similar amounts. An equivalent percentage rise in uropepsin output in normals was observed only after the daily administration of massive dosage (200 to 300 mg.) of glucocorticoids (table 4).

The uropepsin excretion in patient R.E. with Addison's disease increased from control levels of 270 units to 3,118 units after five days of 25 mg. of oral cortisone daily. On a maintenance dose of 25 mg. daily for three months the uropepsin excretion remained elevated (3,910 units). A simi-

TABLE 2

Uropepsin and Adrenal Steroid Excretion in the Normal Subject and in Patients with Addison's and Cushing's Disease

	Number of Patients	Mean Uropepsin Excretion (units/24 hours)	17-Ketosteroid Excretion (mg./24 hours)	17-Hydroxy-corticoid Excretion (mg./24 hours)
Normal	265	3670 (S.E. ± 159)	10.0–15.0	5.0–6.0
Addison's disease				
Untreated	12	540 (S.E. ± 109)	3.7	less than 1.0
Glucocorticoid Replacement therapy	11	4080	—	5.0
Cushing's disease	11	7020 (S.E. ± 1233)	16.4	23.5

TABLE 3

Uropepsin and 17-Ketosteroid Excretion in Addison's Disease Patients

Patient	Uropepsin Excretion (units/24 hours)	17-Ketosteroids (mg./24 hours)
C. O.	840	3.5
D. E.	750	4.6
V. I.	1160	3.8
R. E.	310	4.4
C. N.	80	4.3
M. O.	190	2.1
T. H.	40	7.0
B. L.	610	1.6
M. C.	840	5.3
T. E.	380	2.5
P. E.	280	1.8
P. I.	1020	—
Mean	540 ± 109	3.7 ± 0.5

larly marked response to small doses of glucocorticoids was observed in five other addisonian patients within two to 17 days (table 4). Patients with normal adrenal function demonstrated no significant increase in uropepsin excretion while receiving 50 mg. cortisone daily. The gastric sensitivity to cortisone on the part of the addisonian may explain the high average level of 4,080 units demonstrated by the 11 patients on steroid replacement therapy in doses varying from 12.5 to 50 mg. daily (table 2).

Cushing's Disease: In contrast to the low uropepsin excretion seen in Addison's disease, 11 patients with adrenal or pituitary hyperactivity (Cush-

TABLE 4

Uropepsin Response to Glucocorticoid Therapy in Addison's Disease and in Normal Subjects

Case	Uropepsin (units/24 hours)		Glucocorticoid Therapy	
	Control	During Glucocorticoid Therapy	Dosage	Duration
Addison's Disease				
R. E.	270	3,120	Cpd. E 25 mg.	5 days
		3,910	Cpd. E 25 mg.	3 months
M. O.	190	3,620	Cpd. B 50 mg.	6 days
C. O.	700	2,640	Cpd. E 25 mg.	2 days
		7,810	Cpd. E 25 mg.	2 years
P. I.	1,020	3,540	Cpd. F 50 mg.	3 days
M. C.	840	3,520	Fluorohydrocortisone 0.5 mg.	17 days
T. E.	380	1,900	Cpd. E 12.5 mg.	10 days
Normal Subjects				
1	2,260	3,230	Cpd. E 50 mg.	3 days
2	1,730	2,110	Cpd. E 50 mg.	4 days
3	3,500	11,150	Cpd. E 200 mg.	3 days
4	3,770	11,940	Cpd. F 300 mg.	2 days
5	3,820	15,190	Cpd. F 300 mg.	3 days

ing's disease) demonstrated significantly elevated uropepsin levels, varying from 3,300 to 26,000 units, with a mean of 7,020 units, a rise of approximately 100% above the normal. The excretion of urinary 17-hydroxycorticoids in this group averaged 23.5 mg. per 24 hours, and the 17-ketosteroids 16.4 mg. per 24 hours (table 2).

Bilateral Adrenalectomy: The response of the stomach to the adrenal steroids observed in the addisonian patients is also clearly demonstrated in patients following bilateral adrenalectomy. The level of uropepsin excretion appears to be related to the dose of cortisone or Compound F administered. Patient H. A., for example (figure 1), excreted 4,670 units of uropepsin prior to bilateral adrenalectomy for hypertension. After adrenalectomy the uropepsin excretion rose to 8,390 units during the administration of a total of 750 mg. of cortisone over a five day period. When the cortisone was reduced to a maintenance dose of 50 mg. daily the uropepsin gradually fell to 4,310 units 16 days later, and then decreased further to 1,600 units as the cortisone dose was reduced to 25 mg. daily for the following 14 days. This patient demonstrates a parallelism between cortisone dosage and uropepsin excretion, after bilateral adrenalectomy, with a return

EFFECT OF STEROID REPLACEMENT THERAPY
UPON UROPEPSIN EXCRETION AFTER ADRENALECTOMY

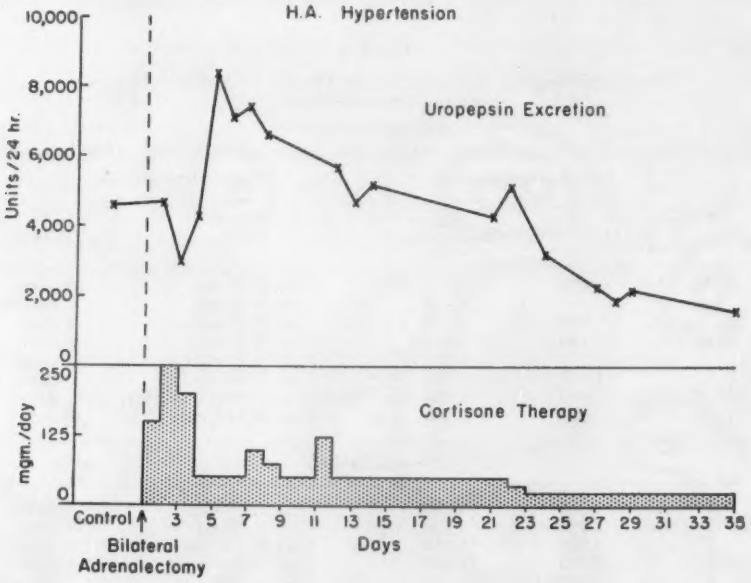

FIG. 1.

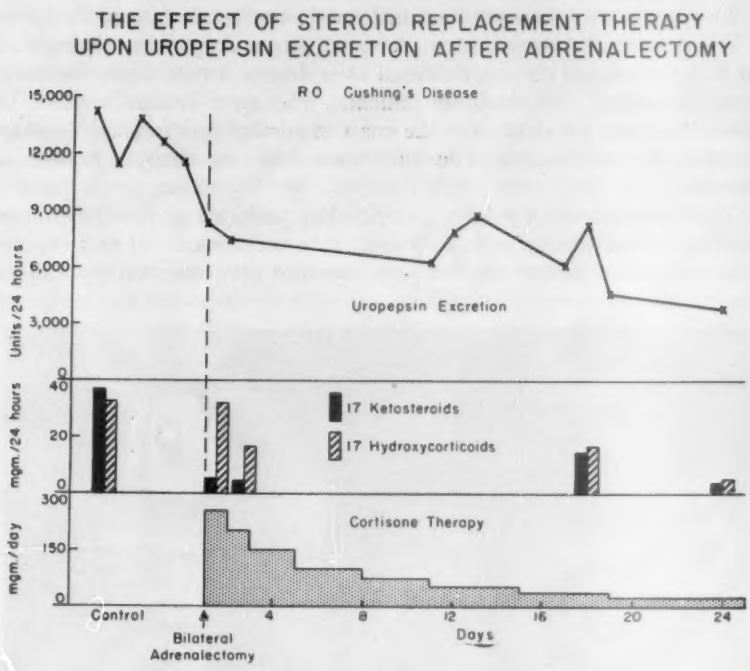

FIG. 2.

to preoperative levels of uropepsin on a maintenance dose of 50 mg. of cortisone.

A similarly close correlation between cortisone administration and uropepsin excretion in the postadrenalectomy state was noted in Patient R.O. (figure 2). The original uropepsin excretion in this patient with Cushing's disease prior to adrenalectomy averaged 12,190 units, with a ketosteroid excretion of 36.9 mg. and a hydroxycorticoid excretion of 32.4 mg. Following bilateral adrenalectomy the uropepsin excretion on the second day fell to 7,500 units on a dosage of 200 mg. of cortisone. As the dose of cortisone was gradually decreased to 25 mg. a day over a period of 24 days, the uropepsin excretion fell to 3,850 units, reflecting optimal replacement dosage.

Development of Peptic Ulcer in Patients with Addison's Disease Receiving Adrenal Steroid Therapy

Seven patients with Addison's disease developed a peptic ulcer de novo or a symptomatic exacerbation of a previously existing ulcer while on maintenance cortisone therapy.

Two addisonian patients, one male and one female (cases N. L. and A. T.), developed chronic gastric ulcer, and two male patients (cases V. O. and P. I.) developed chronic duodenal ulcer disease for the first time during steroid treatment. Three other patients, who were known to have had chronic duodenal ulcers prior to the onset of adrenal insufficiency, developed a symptomatic reactivation of the ulcer while receiving cortisone replacement therapy.

The development of a large gastric ulcer perforating into the pancreas in a 24 year old woman is an extremely rare occurrence. It was observed in an addisonian patient while on maintenance cortisone therapy (25 mg.

FIG. 3. Large gastric ulcer in a 24 year old addisonian woman who received 25 mg. cortisone daily for three years.

daily) for three years, and demonstrates the sensitivity of the gastric mucosa to administered steroids (figure 3). This is also illustrated in another patient with Addison's disease who developed a gastric ulcer while receiving only 12.5 mg. of cortisone daily for three years. These two patients presented uropepsin levels of 3,000 and 1,900 units per 24 hours, respectively, which are markedly elevated over the average value of 540 units found in the untreated Addison's disease group (cases N. L. and A. T.).

A third case was that of a 57 year old male with known Addison's disease of 18 years' duration who developed an acute duodenal ulcer with

bleeding following three years of cortisone therapy varying from 12.5 to 25 mg. daily. Uropepsin excretion in this patient varied from 3,000 to 4,800 units per 24 hours (case V. O.).

The fourth patient was a 34 year old white male with known Addison's disease of 18 years' duration who had been treated for four years with cortisone, 25 mg. daily. This patient (P. I.) died suddenly of unknown cause and at autopsy two chronic duodenal ulcers measuring 1 by 2 cm. were noted just distal to the pylorus (figure 4). Uropepsin studies done two years prior to his death revealed an excretion of 3,540 units per 24 hours.

The three patients with reactivation of symptoms of previously existing ulcers demonstrated relatively high uropepsin excretion rates in the duodenal ulcer range, varying from 4,000 to 8,000 units per 24 hours.

FIG. 4. Duodenal ulcer in a 34 year old male addisonian maintained on 25 mg. cortisone daily over a four year period.

CASE REPORTS

Case 1. N. L., a 24 year old white female with Addison's disease of four years' duration, was maintained for three years upon adrenal hormone therapy consisting of oral cortisone, 25 mg. daily, and desoxycorticosterone trimethyl acetate, 60 mg. intramuscularly at monthly intervals. There was no previous ulcer history. Ten months before admission the patient experienced one transient episode of burning epigastric pain, relieved by milk. Following this she was free of gastrointestinal symptoms until five months before admission, when there was a recurrence of similar distress, accompanied by vomiting, which persisted and increased in severity for two months before admission. X-ray examination on admission revealed a large prepyloric ulcer, 1 by 3 cm. in diameter, on the posterior wall, with probable inflammation of the pancreas and periduodenitis secondary to penetration (figure 3).

The patient was placed on ulcer management and maintained on cortisone, 25 mg. daily, with gradual subsidence of symptoms. X-rays seven months later still revealed an ulcer, 0.7 by 1.5 cm. in diameter. The most recent examination (one year following the initial demonstration of the lesion) showed complete healing with minimal residual scarring.

Case 2. A. T., a 61 year old white male with Addison's disease of 16 years' duration, had been treated from 1937 to 1950 with periodic subcutaneous implantation of desoxycorticosterone pellets. For three years before admission he also received 12.5 mg. of cortisone daily by mouth. Two months prior to admission the patient first noted the onset of vague epigastric distress, increasing in severity, and two episodes of melena two weeks before admission. There was no history of previous epigastric distress.

Two roentgenologic examinations revealed a small prepyloric ulcer on the lesser curvature which appeared benign. Gastroscopy also demonstrated a small gastric ulcer, approximately 0.5 in. in diameter.

The patient was placed on a strict ulcer regimen and a reduced dosage of oral cortisone (6.25 mg. per day). Reëxamination by both fluoroscopy and gastroscopy three weeks later failed to reveal any evidence of the previously observed lesion. The patient remained asymptomatic while on ulcer management.

Case 3. P. I., a 34 year old white male with known Addison's disease since 1936, had been maintained on DOCA pellet implantation from 1938 until 1950, at which time oral cortisone, 12.5 mg. twice daily, was added. He did well on this therapy except for excessive psychic stimulation which was felt to be due to cortisone administration. Cortisone was therefore reduced to 12.5 mg. daily in January, 1951. From that time until his death in April, 1954, he was maintained on daily cortisone therapy varying from 12.5 to 25 mg.

He was hospitalized in December, 1953, because of an acute psychotic episode characterized by catatonia attributed to an overdosage of cortisone. This episode subsided spontaneously over a one week period and there was a return of his normal mental state.

Four months following discharge he died suddenly at home. No definite cause of death could be ascertained at autopsy. However, two oval-shaped benign chronic ulcers measuring 1 by 2 cm. were found in the duodenum just distal to the pylorus. There was no record of previous peptic ulcer or epigastric complaints.

Case 4. V. O., a 57 year old white male steel worker, had first been diagnosed as having Addison's disease 18 years previously, and was treated by periodic DOCA pellet implantations, Percorten and added salt for the next 15 years.

Approximately three years before admission hypothyroidism was detected and therapy instituted consisting of 30 mg. of thyroid extract daily, oral cortisone, 25 mg. daily, and intramuscular desoxycorticosterone trimethyl acetate at monthly intervals. There was no history of previous epigastric distress.

Seven months before admission he suddenly developed weakness and melena and was admitted to an outside hospital, where x-rays revealed an acute active duodenal ulcer. He was treated with an ulcer diet, antacids and antispasmodics along with his regular steroid therapy, and the bleeding stopped promptly. He remained asymptomatic until one week before admission, when, following a dietary indiscretion, he developed a steady localized epigastric pain with considerable belching. The pain disappeared following four days of self-medication with diet and antacids, and three days later he was admitted for further investigation.

X-rays on admission revealed a chronic ulcer deformity of the duodenal cap, but no actual ulcer crater could be demonstrated. He remained asymptomatic in the hospital while on combined ulcer management and daily cortisone therapy.

Discussion

The findings reported in this investigation corroborate previous studies on the rôle of the adrenal cortex in maintaining normal gastric secretory activity, and further extend these observations in the human to include pepsin output (uropepsin). The low uropepsin excretion in the untreated addisonian patient and the rapid return to normal levels on initiating glucocorticoid therapy tend to demonstrate that it is the endogenous secretion of these hormones (as exemplified by Compounds E, F and B in this study) which is primarily responsible for the adrenal effect upon the stomach.

The relatively greater response of the Addison's disease and postadrenalectomy patients to minimal glucocorticoid dosage (12.5 to 50 mg. daily), as compared to normal subjects receiving similar amounts, favors the hypothesis that in conditions of relative or absolute adrenal insufficiency the peptic cells are more sensitive to the administered hormone. The steroid dosage required to produce an equivalent percentage increase in uropepsin output in the normal is usually in the range of 200 to 300 mg. per day. This observation has certain clinical significance in the treatment of Addison's disease patients, since with excessive replacement therapy gastric hypersecretion and ulceration may occur, as noted in the case presentations.

Griep and Buchholz [32] have also reported such an occurrence in an Addison's disease patient who had a history of a chronic duodenal ulcer antedating the onset of her adrenal insufficiency. On receiving large doses of cortisone (3,900 mg. over a 12 day period) to correct an episode of adrenal crisis, this patient developed an acute perforation of a duodenal ulcer 12 days after intensive therapy was begun. Similarly, Engel [33] has described a patient with known Addison's disease of four years' duration who developed a small prepyloric ulcer while on cortisone (25 mg. daily) over a two and one-half year period. The ulcer healed within six weeks after discontinuing cortisone while the patient was maintained on ulcer management. Although histamine anacidity had been demonstrated two and one-half years previously, before cortisone therapy was instituted, a repeated gastric analysis at the time the ulcer was diagnosed revealed 30 c.u. free acid after histamine. Potentiation of gastric acidity with cortisone has been demonstrated previously in Addison's disease.[18]

The discrete chronic peptic ulcer developing on hormone therapy should be distinguished from superficial gastrointestinal ulcerations occasionally observed in patients with acute adrenal insufficiency. During acute adrenal crisis in the human, multiple superficial ulcerations involving the pyloric region of the stomach, the first part of the duodenum, jejunum and occasionally the rectum are not uncommon. These lesions heal promptly with adrenal replacement therapy and are usually not demonstrable by roentgen examination.

Similar acute gastric lesions occurring during absolute or relative adrenal insufficiency in the human can be produced experimentally by severe stress in animals following the removal of the adrenal glands, and probably result from vascular stasis and cellular damage accompanying the state of shock, dehydration and electrolyte imbalance which characterizes acute adrenal insufficiency. Selye [84] noted that these acute ulcers following stress in the adrenalectomized animal could be prevented by suitable replacement therapy with adrenocortical hormones.

The superficial gastrointestinal ulcerations observed during acute adrenal crisis in humans, or following bilateral adrenalectomy in animals, present an entirely different picture from the gastric and duodenal ulcers produced during excessive cortisone administration in the Addison's disease patient or in normal subjects. The steroid-induced lesions are typical chronic ulcers developing in patients receiving adequate replacement therapy and in good electrolyte and metabolic balance. The ulcers appear to be related to gastric hypersecretion, as evidenced by the exaggerated uropepsin response to small doses of cortisone in addisonian patients, and the high levels of gastric acid, pepsin and uropepsin, often in the ulcer range, observed during ACTH or cortisone administration in normal individuals. Other factors, such as alterations in the mucus barrier, interference with tissue repair, and decreased tissue resistance secondary to vascular and metabolic disturbances, should be considered.

Epigastric distress induced during glucocorticoid replacement therapy in Addison's disease is an indication for antacid therapy, particularly in the presence of a high uropepsin excretion.

Summary

The present study emphasizes the significance of pituitary-adrenal influences upon the stomach, as evidenced by the following observations:

1. A low incidence of chronic peptic ulcer and a decrease in gastric acidity are characteristic findings in patients with Addison's disease.

2. Bilateral adrenalectomy reduces the gastric volume and acidity in experimental animals and is accompanied by an associated involution of the gastric tubular cells.

3. A low uropepsin excretion is invariably found in Addison's disease patients, with a return to normal or elevated levels during replacement glucocorticoid therapy.

4. An increased uropepsin excretion occurs in states of adrenal hyperactivity (Cushing's disease).

5. There appears to be an exaggerated gastric response to administered adrenal steroids in the addisonian and in patients following bilateral adrenalectomy.

6. Chronic peptic ulcer de novo or reactivation of symptoms of a previously existing ulcer has been demonstrated in Addison's disease patients receiving cortisone replacement therapy.

7. Antacid therapy may be indicated in Addison's disease patients maintained on long-term glucocorticoid therapy.

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SUMMARIO IN INTERLINGUA

Le relation inter le glandula adrenal e le stomacho es un facto establite, viste le augmento del secretion de acido gastric e de pepsina durante stimulation adrenal. Le involvimento del glandula adrenal in le pathogenese de ulcere peptic es manifeste per le facto que le disveloppamento o le reactivation de ulceres ha essite observate durante cursos therapeutic de ACTH o steroides adrenal. In plus, le existentia de un relation adreno-gastric es suggerite per studios correlative del function gastric e adrenal in stato de reposo e post stimulation adrenal.

Le presente studio esseva interprendite pro obtener un evalutation additional del influentias adrenal super le stomacho in statos de hypo- e de hyperfunction adrenal e post adrenalectomia bilateral. Le excretion urinari de uropepsina esseva usate como indice del activitate secretori del stomacho. Le function adrenal esseva studiate simultaneemente per mesurationes del steroides urinari.

Dece-duo patientes con morbo de Addison qui non recipeva therapias glucocorticoide demonstrava un marcate reduction del excretion de uropepsina (nivello medie: 500 unitates per 24 horas), parallel a un reduction del nivello urinari de steroide adrenal. Le initiation de therapia substitutive a glucocorticoide resultava in un retorno del excretion de uropepsina a nivellos normal o supranormal (dependente del dosage substitutive).

In 11 patientes con hyperactivitate adrenal o pituitari il habeva un elevation significative del excretion de uropepsina (nivello medie: 7.000 unitates per 24 horas) e un simile augmento in le excretion de steroide adrenal.

Post adrenalectomia adrenal il habeva un nette correlation inter le dosage del therapia substitutive de glucocorticoide e le excretion de uropepsina. Quando le doses del therapia substitutive esseva reducite, un reduction parallel del nivello de uropepsina esseva observate.

Ulcere peptic es extrememente rar in non-tractate morbo de Addison. Tamen, ulceres gastric o duodenal se disveloppava durante le curso de iste studios in septe patientes de morbo de Addison qui recipeva prolongate therapias substitutive de cortisona. Elevate nivellos de uropepsina esseva notate in iste patientes.

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IDIOPATHIC PERICARDITIS *

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Idiopathic pericarditis is being diagnosed with increasing frequency. This paper is a review of the 23 cases admitted to The Montreal General Hospital and the Queen Mary Veterans Hospital between the years 1945 and 1955. Twenty of these cases were diagnosed after 1950. An attempt is made to relate symptoms, signs and laboratory findings to clinical diagnosis.

The disease is a perplexing entity. Pathogenesis is little understood, and diagnosis may present considerable difficulty. Although many descriptions of the disease have appeared in recent literature, only three other series [1, 2, 3] have included more cases than are here presented.

Individual cases are summarized in table 1.

The criteria for selection of cases in this series were taken to be:

1. Presence of pain.
2. A pericardial friction rub, and/or
3. A characteristic electrocardiographic pattern.
4. No specific demonstrable cause of pericarditis.

All cases in which the diagnosis was doubtful were excluded. Patients with a previous history of rheumatic fever, and patients who subsequently were known to have developed rheumatic fever, also were omitted.

Age and Sex Distribution

All patients in this series but one were between 15 and 45 years of age. Of the 15 cases from The Montreal General Hospital, 11 were male and four were female. The eight cases admitted to the Veterans Hospital were obtained from military personnel, and all were males.

Symptoms

1. General Symptoms: Chills, fever, malaise, headache and anorexia were frequently encountered.

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TABLE 1

Twenty-three Cases of Idiopathic Pericarditis Were Admitted to the Montreal General Hospital and the Queen Mary Veterans Hospital in the Years 1945 to 1955

Case No.	Age and Sex	Symptoms	Max. fever	Max. pulse	Physical examination	Max. WBC	ESR	Investigations		Therapy	Outcome
								Chest x-ray and fluoroscopy	Electrocardiogram		
1	21, m	URI, cough, shortness of breath. Sharp, squeezing precordial, left shoulder and back pain, aggravated by breathing and coughing.	98°	80	Loud to-and-fro pericardial rub at apex on 4th day, lasting 17 days. Lymphadenopathy, pharyngitis.	5,200	N	Normal.	Slight ST elevation in V_2, V_4. Later T wave inversion in 3.	—	Well at 4 weeks.
2	18, m	Aching precordial, retrosternal, right and left shoulder pain, aggravated by breathing.	100.8	88	Moderate to-and-fro pericardial rub at left sternal border on 1st day, lasting 2 days. Lymphadenopathy, pharyngitis, ?cyanosis.	18,800	+	Normal.	Questionable ST elevation in 2, V_2, V_4, V_6.	Strep.	Well at 1 week.
3	35, m	Shortness of breath. Aching, cutting precordial and left shoulder pain, aggravated by breathing.	100	92	Loud pleuropericardial rub heard only on 21st day. Pleural component remained 7 days. Dull left base; signs of parenchymal lung disease. Lymphadenopathy.	10,200	++	Left pleural effusion. Left vent. enlargement. Pulm. congestion.	—	Strep. and PAS.	Well at 7 weeks.
4	31, m	Conjunctivitis. Sharp precordial, epigastric and neck pain, aggravated by breathing.	100.2	100	—	10,000	++	Peric. effusion, left vent. enlargement, and a right pleural effusion.	ST elevation in 1, 2, AVF, V_6. Later T wave inversion in 1, 2, AVL V_2, V_4, V_6 with return to normal of ST.	Strep., pen., cortisone. Peric'tesis: 100 c.c. straw-colored fluid (10th day).	Well at 3½ weeks. 12 recurrences over 4 years.
5	42, f	Shortness of breath. Sharp retrosternal, left sternal border, left shoulder and arm, back and neck pain, aggravated by breathing.	101	136	—	12,500	++	Left vent. enlargement, returning to normal. Right parenchymal lung disease.	ST elevation in 1, 2, V_2, V_4, V_6. T wave changes in all leads lasting 1 month.	Sulfas, Aureo., Chloromycetin	Well at 7½ weeks.
6	40, m	URI, vomiting. Sharp retrosternal, epigastric and left shoulder pain, aggravated by breathing.	101	124	—	15,500	++	Normal.	ST markedly elevated in 1, 2, AVL, AVF, V_2, V_4, V_6, depressed in AVR. Later return to normal with T wave inversion in 1, 2, 3, V_2 V_4, V_6, AVF.	—	Well at 6 weeks.

TABLE 1—*Continued*

Case No.	Age and Sex	Symptoms	Max. fever	Max. pulse	Physical examination	Max. WBC	ESR	Investigations		Therapy	Outcome
								Chest x-ray and fluoroscopy	Electrocardiogram		
7	29, m	Nausea, vomiting, and shortness of breath. Twisting retrosternal, left chest and left arm pain.	98.3	68	Lymphadenopathy.	7,500	++	Normal.	Slight ST elevation in 1, 2, V_2, V_4, V_6.	—	Well at 1½ weeks. 3–4 recurrences.
8	27, m	Aching, squeezing precordial, epigastric, left chest, left and right shoulder and arm pain.	98.3	66	—	6,650	+	Normal.	ST markedly elevated in 1, 2, V_2, V_4, V_6 with later return to normal.	Terramycin	Well at 2 weeks.
9	27, m	URI, cough. Deep retrosternal, precordial, epigastric, and left shoulder pain, aggravated by coughing.	101	120	Pronounced to-and-fro pericardial rub at apex and left sternal border on 3rd day, lasting 3 days. Lymphadenopathy, pharyngitis,	7,200	+	Transient cardiac enlargement.	Slight ST elevation in 1, 2, V_2, V_4, V_6. T wave changes.	Strep., pen.	Well at 2 weeks. 2 recurrences in 4 months.
10	65, f	Severe retrosternal, left and right shoulder, neck and cheek pain.	101	96	Pericardial rub at left sternal border on 2nd day, recurring after peric'teses on 7th and 10th days. Pharyngitis.	16,600	—	Peric. effusion. Left parenchymal lung disease.	Variation in T waves with increasing voltages after peric'tesis.	Pen. Peric'tesis: 150 c.c. (5th day), 50 c.c. (12th day), straw-colored.	Well at 2 weeks.
11	24, m	Sharp retrosternal, left and right shoulder, and diffuse chest pain, aggravated by coughing and breathing.	100	80	Pericardial rub for a few hours on 1st day. Marked.	12,600	N	Normal.	Questionable ST elevation in 2, 3. Increasing T wave in 1, 2, with inversion in 3.	—	Well at 1½ weeks. 2 recurrences in 2½ years.
12	17, f	Vomiting and shortness of breath. Retrosternal and and back pain, aggravated by breathing.	101	88	Scratchy, to-and-fro pericardial rub, mid-sternum, on 2nd day, lasting 1 day. Pharyngitis, neck vein engorgement.	13,200	+	Left pleural effusion and parenchymal lung disease.	ST elevation in 1, V_6.	Sulfas, pen.	Well at 1 week.

TABLE 1—*Continued*

Case No.	Age and Sex	Symptoms	Max. fever	Max. pulse	Physical examination	Max. WBC	ESR	Investigations		Therapy	Outcome
								Chest x-ray and fluoroscopy	Electrocardiogram		
13	21, m	URI, shortness of breath. Sharp retrosternal, neck, left shoulder and arm pain, aggravated by breathing.	100	108	Pericardial rub at left sternal border on 1st and 7th days. Dullness left lung base.	9,300	++	Normal.	ST elevation in all leads except AVR, which was depressed. Slight T wave changes.	Aureo.	Well at 5 weeks.
14	22, m	Nausea, vomiting, shortness of breath. Burning retrosternal, neck, left shoulder and arm pain, aggravated by breathing.	102	150	Loud, scratchy, to-and-fro pericardial rub at left sternal border, following peric'tesis on 30th day, lasting 5 days. Dullness left lung base; Ewart's sign; cyanosis; neck vein engorgement; paradoxical pulse.	19,000	—	Peric. effusion. Left pleural effusion.	Following peric'tesis marked elevation in 1, 2, AVL, AVF, V_2, V_6 and increase in all T wave voltage.	Strep. Pen. Peric'teses: 410 c.c. etc.	Death at 5 weeks.
15	44, m	Nausea, shortness of breath. Sharp, squeezing retrosternal, precordial, epigastric, left and right shoulder pain, aggravated by breathing.	99.2	80	To-and-fro pericardial rub at left sternal border on 1st day, lasting 3 days.	12,000	N	Normal.	Slight elevation of ST in 2, V_2, V_4, V_6, returning to normal. Incomplete RBBB, T wave changes.	—	Well at 2 weeks.
16	36, m	Squeezing retrosternal pain, occurring only on deep inspiration.	98.3	100	Parenchymal lung disease.	12,000	+	Left parenchymal disease.	Marked ST elevation in 1, 2, AVF, V_2, V_4, V_6, less in 3. Return to normal after 3 days, when T waves became lower.	—	Well at 3 weeks.
17	19, m	URI, cough. Aching retrosternal pain, aggravated by breathing.	103	136	Loud, squeaky pericardial rub, medial to apex, on 4th day only. Dullness both bases; signs of parenchymal lung disease. Lymphadenopathy, pharyngitis.	7,000	N	Left and right parenchymal lung disease.	Non-specific changes.	Pen., Aureo., Terramycin.	Well at 6 weeks.

TABLE 1—*Continued*

Case No.	Age and Sex	Symptoms	Max. fever	Max. pulse	Physical examination	Max. WBC	ESR	Investigations		Therapy	Outcome
								Chest x-ray and fluoroscopy	Electrocardiogram		
18	38, m	URI, shortness of breath. Squeezing retrosternal, diffuse precordial, chest and back pain, aggravated by breathing.	102	100	—	10,300	+	Normal.	Slight ST elevation in 1, V_2, V_4. T wave decreased or negative in 1, 2, V_1, V_2, V_3, V_4, V_5, V_6.	—	Well at 1½ weeks. 5 recurrences in 1 year.
19	31, m	Aching retrosternal, left shoulder and neck pain, aggravated by breathing.	98 (prev. up)	94	—	7,400	+	Normal.	ST elevation in 1, 2, 3. Later T wave inversion.	—	Well at 4 weeks. 3 recurrences in 6 months.
20	33, m	URI, cough, shortness of breath. Squeezing epigastric, retrosternal, left shoulder and back pain, aggravated by breathing.	102	140	Pericardial rub at apex on 7th day, lasting 3 days. Paradoxical pulse; cyanosis. Lymphadenopathy.	13,600	+	Left pleural effusion. Cardiac enlargement.	T waves became negative in all leads but AVR, returning to normal at end of 4 weeks.	—	Well at 2 weeks. 4 recurrences in 3 months.
21	28, m	URI, cough, shortness of breath. Sharp right arm pain, aggravated by coughing.	101	110	To-and-fro pericardial rub on first day only. Right pleural rub; dullness both bases; signs of parenchymal lung disease. Pharyngitis.	13,500	++	Bilateral pleural effusion. Right parenchymal lung disease. Minimal cardiac enlargement.	T waves biphasic in 1, 2, 3, AVF, V_6, notched in V_4.	Strep., pen., Chloromycetin. Thorac'teses: 2500 c.c. straw-colored fluid obtained.	Well at 10 weeks.
22	45, m	Retrosternal pain, aggravated by breathing.	103	106	?pericardial rub. Right pleural rub; dullness left base; signs of parenchymal lung disease.	13,300	++	Bilateral pleural effusion. ? pericardial effusion or cardiac enlargement.	Negative T in 1, 2, 3, AVF, V, V, V, with some serial changes.	Strep., PAS. Thorac'tesis: 5 c.c. straw-colored fluid obtained.	Well at 8 weeks. 2 recurrences in 2 years.
23	19, f	URI, cough, shortness of breath. Aching retrosternal, left chest, and back pain.	102	100	Pericardial rub on 2nd day. Pharyngitis.	—	—	—	Compatible with pericarditis.	Pen.	Well at 4 weeks.

2. Upper Respiratory Infection: Upper respiratory infections, commonly consisting of cough, coryza and sore throat, preceded or coincided with the onset of pericarditis in nine cases.

3. Pain: Pain was the predominant symptom of pericarditis and was present in all cases.

The onset of the pain was usually sudden, although on occasion it began as a mild discomfort and increased over a period of days. The intensity varied from a mild ache to a severe, incapacitating pain. It was continuous in all but one case. Breathing aggravated the pain in 18 cases. Cough alone accentuated distress in one further case. A wide variation in the nature of the pain was noted. "Sharp," "aching," "heavy," "cutting," "squeezing," "twisting" and "burning" were the descriptive terms applied.

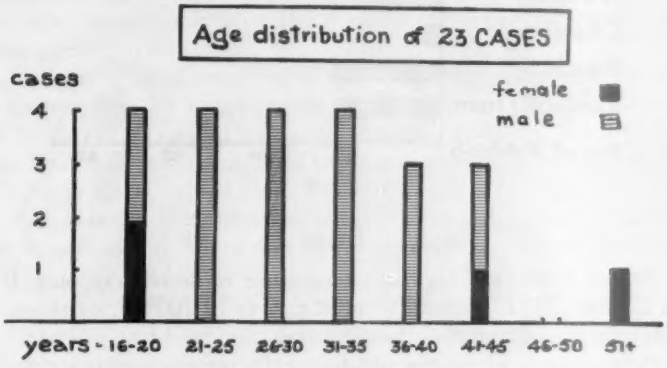

FIG. 1.

Frequently the nature of the pain changed during the course of the illness. Sharp or cutting pain often became more aching and persistent at a later stage.

The location was widespread. Chest pain was present in all patients but one (case 21); this was retrosternal in 18, precordial in eight, left anterior in three and diffuse in two. All sites are summarized in figure 2.

4. Dyspnea: Shortness of breath was a prominent symptom in 12 out of 23 patients. The severity varied greatly, from those who noted only slight dyspnea on exertion to others who were markedly short of breath at rest. In one patient, rapid, shallow breathing was caused by severe pain on respiration.

5. Gastrointestinal Symptoms: Nausea and vomiting occurred in five cases and were sometimes noted before the pericarditis became manifest. Diarrhea preceded one case.

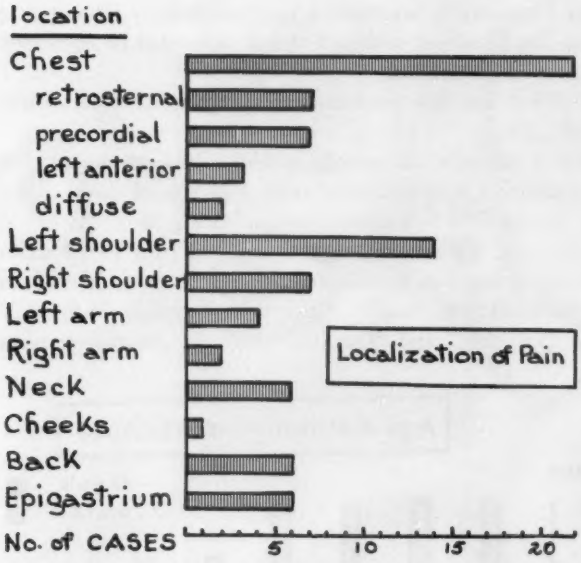

FIG. 2.

SIGNS

1. Fever: While the highest temperature recorded was only 103° F. (cases 17 and 22), 17 patients showed a fever of 100° F. or more. Four were afebrile throughout their hospital stay.

2. Pulse Rate: Tachycardia was frequently present in this series. Thirteen of the patients showed a pulse rate of over 100, and six of these had rates of 120 or more. A so-called "paradoxical pulse" with cyanosis was noted in two patients, and in one of these there was neck vein engorgement as well. This latter patient (case 14) had a massive pericardial effusion confirmed by aspiration, and the other (case 22) showed a gross enlargement of the cardiac shadow.

3. Blood Pressure: In only one patient (case 14) was there significant change in the blood pressure. In this patient the admission blood pressure was 90/60 mm. Hg, and clinical and laboratory findings indicated cardiac tamponade. Shortly after admission the blood pressure became imperceptible. Following pericardicentesis the pressure returned to 100/70 mm. Hg.[4]

4. Pharyngitis: Examination revealed pharyngitis in eight patients.

5. Lymphadenopathy: Eight patients were noted to have lymphadenopathy. This was frequently generalized in distribution.

6. Pericardial Friction Rub: The pericardial friction rub was by far the most important sign of pericarditis and was heard in 15 cases on one or more

occasions. Of the eight patients in whom no friction rub was heard, three were not examined until after the fifth day of illness.

A rub was heard within a few hours of the onset of symptoms in some patients and as late as 42 days in another. Although the average duration was two to three days, in one patient it lasted for only a few hours, and in another it was heard for 17 days. Pericardial friction rubs were usually best heard to the left of the sternal border or just medial to the apex. Positioning was sometimes required to bring out the rub. The quality was variously described as scratchy, squeaky or harsh. Typically, it was of the to-and-fro variety.

In two cases the rub ceased to be heard with the formation of significant effusion. In the first of these (case 10), the rub was present early in the disease, disappeared with the formation of the effusion, and reappeared on two occasions immediately following pericardicentesis. In the second (case 14), it was detected only after the removal of 410 c.c. of fluid. Ewart's sign was present in this case.

7. Pleuritis: Pleural involvement was a common accompaniment of idiopathic pericarditis. A pleural friction rub was heard in four of the series, on the left in two cases and on the right in two cases. Clinical findings of pleural effusion were noted in three cases, and radiologic findings of effusion were found in six.

8. Pneumonitis: Clinical signs of parenchymal lung involvement were present in two cases. There was radiologic evidence in three further cases.

Laboratory and Clinical Investigations

1. Hematological Findings: A leukocytosis of 10,000 cells per cubic millimeter or more was noted in 15 patients. None of the counts exceeded 20,000, and leukopenia was not found. The differential white blood cell count showed a wide variation, and no consistent pattern was apparent. Of the 20 patients who had erythrocyte sedimentation rates determined, eight showed marked elevation, an equal number had a moderate elevation, and only four were within normal limits.

2. Electrocardiographic Changes: Eight patients in this series showed characteristic changes of ST segment elevation and subsequent T wave changes. In four patients typical T wave changes were observed without ST elevation. Nine further cases showed nonspecific or questionable ST segment or T wave changes.

3. Radiologic Findings: Chest x-rays were taken in all but one patient. In several cases serial x-rays were obtained and, in some, chest fluoroscopy was performed. Nine cases out of the 23 showed enlargement of the cardiac silhouette, and in three of these cases a diagnosis of pericardial effusion was confirmed by aspiration.

A left-sided pleural effusion was noted in five patients, and in two of these it was present bilaterally. One patient had a right-sided effusion only.

Parenchymal infiltration of the lung was noted in five patients, three on the left, one on the right and one bilateral.

4. Pericardicentesis: Pericardicentesis was performed in three patients. In the first (case 4), 100 c.c. of a straw-colored fluid were removed on the tenth day. The fluid was sterile and contained only leukocytes. The second patient (case 10) had a pericardial tap performed on the fifth day of illness and repeated on the twelfth day. This fluid was also straw-colored.

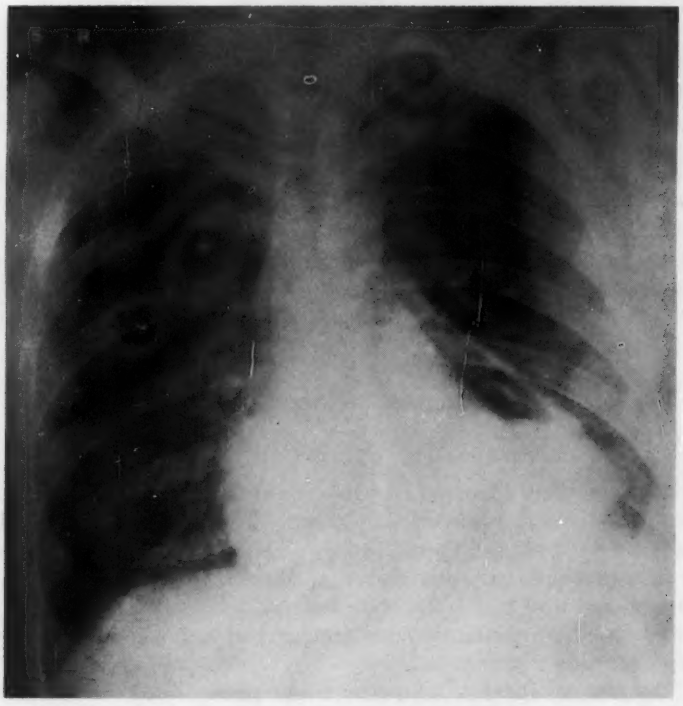

FIG. 3. *Case 14.* Chest x-ray following the aspiration of 410 c.c. of sanguineous fluid and the injection of air into the pericardial space.

The only fatal case (case 14), which has been reported in detail,[4] was tapped on two occasions about a month after the onset of symptoms. A total of 960 c.c. of a sanguineous fluid was removed, and a further 1,000 c.c. were found at autopsy.

5. Thoracentesis: In one patient (case 21) thoracentesis was performed and a total of 2,500 c.c. of a straw-colored fluid was removed from the right and left pleural spaces.

Etiology

Idiopathic pericarditis has been reported frequently in association with virus infection elsewhere in the body. The literature describes cases following upper respiratory disease, virus pneumonia, epidemic myositis and infectious mononucleosis.[5, 6, 7, 8, 9, 10] In these instances the course is usually in keeping with that of a virus infection. Attempts to culture virus organisms from the pericardial effusion, however, have never been successful. The theory that contact transmission occurs has been expressed.[8, 11]

Pericardial response to an offending allergen is a rare cause, but has been well described in the literature. Cases have been reported in allergic disease, and following diphtheria and tetanus antitoxin injections.[12, 13] Carmichael et al. consider response to toxins an important etiologic factor, and use the frequency of the pericarditis which occurs in terminal uremia to substantiate the argument.[1] The possible relationship between idiopathic pericarditis and the clinical syndrome of polyserositis has not yet been fully investigated.

Stepman and Owyang state that a tuberculous infection is most often responsible for the development of idiopathic pericarditis.[14]

Dressler has suggested recently that idiopathic pericarditis may be a manifestation of rheumatic disease of the pericardium, and may be identical with the so-called post-commissurotomy syndrome.[15]

Idiopathic pericarditis has been described following a variety of operative procedures not involving the heart.[16, 17]

Bourne suggests that an arteritis can exist in the vessels supplying the pericardium and that, in certain cases, pericardial infarction can occur to produce the clinical picture of pericarditis.[18]

Differential Diagnosis

The diagnosis must be made by careful exclusion of other forms of pericarditis and other diseases causing chest and abdominal pain. Specific causes of pericarditis which must be eliminated include infection (pyogenic and tuberculous), rheumatic fever, the collagen diseases, myocardial infarction, neoplasms (primary and metastatic), uremia and trauma.

In cases where the characteristic friction rub or pathognomonic electrocardiographic changes are present, the diagnosis of pericarditis per se is not hard to make. However, the presence of pain alone introduces a large number of other possibilities, including myocardial infarction, coronary insufficiency, dissecting or other aneurysms, pulmonary hypertension, pneumonia, pleuritis, mediastinitis, pleurodynia, herpes zoster, intercostal neuralgia, diaphragmatic hernia and acute abdominal conditions.

Myocardial infarction is by far the most important and often the most difficult disease to differentiate. The onset, location and radiation of the pain may be similar in both conditions. Both disease states are more com-

mon in males. Symptoms of anxiety, dyspnea and gastrointestinal upset may be manifest in both. Cardiac rate, heart size and heart sounds do not usually help with the diagnosis. The age of the patient, a previous history of angina pectoris or hypertension, a family history of coronary artery disease, or the presence of other predisposing or precipitating factors may help to establish a diagnosis of myocardial infarction. The presence of a gallop rhythm or other cardiac arrhythmia, pulmonary edema, cardiac failure, shock, hiccup or embolic phenomena suggests myocardial infarction. In pericarditis the pain is more often accentuated by breathing or coughing; a preceding history of upper respiratory infection is common, and chills, malaise and headache are frequently present. In idiopathic pericarditis, a friction rub often appears in the first few hours;[1] in myocardial infarction it is seldom present before 36 hours. Fever and erythrocyte sedimentation rate are elevated earlier in pericarditis. Pericardial effusion is rare in myocardial infarction. Pleuritis and pneumonitis occur more frequently in idiopathic pericarditis. Serial electrocardiograms are usually most important in making the diagnosis clear.

It is important to distinguish between idiopathic and rheumatic pericarditis. The actual symptoms and signs of rheumatic pericarditis are those of pericarditis per se. In most cases of rheumatic fever, however, a suggestive history of previous joint involvement can be elicited, and other manifestations of rheumatic disease can be found. The rheumatic fever patient showing clinical evidence of pericarditis frequently also has evidence of characteristic rheumatic valvular disease. The temperature is high, and pneumonia, pleuritis or heart failure may be present. Subcutaneous nodules are said to be especially frequent in rheumatic pericarditis.[19]

Pleurisy, with or without pneumonia, may accompany idiopathic pericarditis, and may mask the latter condition.

Pericarditis can cause abdominal pain, and must therefore be differentiated from all acute abdominal conditions. A careful history, a pericardial friction rub and typical electrocardiographic changes make the differentiation possible.

Pathology

Seven pathologic descriptions appear in the literature. Two of these are surgical, one obtained by biopsy,[2] the other by pericardiectomy.[20] Three patients died in cardiac tamponade during the course of the disease.[4, 21, 22] One patient died receiving anticoagulant therapy.[23] Another patient committed suicide, in an unrelated depression, in the final stages of convalescence.[24]

While only two of the pathologic descriptions are complete, all establish the pericardial nature of the disease. An organizing, nonspecific pericarditis is found. Coronary vessels and myocardium are grossly normal.

Polymorphonuclear leukocyte infiltration of the myocardium adjacent to the epicardium has been described.

Treatment

Divergent opinions have been expressed regarding the efficacy of various specific therapies. Sulfonamides, penicillin, streptomycin, chlortetracycline, oxytetracycline and chloramphenicol have been used.[11, 25, 26, 27] There is no known effective specific treatment.[7, 28]

Corticotropin is said to produce a remission in the course of the disease, and has been used in the treatment of severely ill patients.[29, 30] One patient in this series was given cortisone (case 12). This patient showed symptomatic relief at first, but then actually developed a recurrence while on therapy.

The effective use of an antihistamine (Pyribenzamine) has been described in a case of pericarditis in an allergic patient.[13]

Anticoagulants are definitely contraindicated. One death has been reported following the use of heparin and Dicumarol.[28]

Symptomatic relief should be afforded, and the patient should be placed at bed-rest. The bed-rest should continue until all clinical signs and symptoms of the disease have disappeared.[24, 31]

In cases in which pericardial effusion has developed, careful consideration should be given to the possible occurrence of cardiac tamponade. Pericardicentesis should be undertaken where necessary, and may prove a life-saving measure.[4]

In a case described by Yu et al.[20] a pericardiectomy was done after nearly 5 L. of fluid had been withdrawn from the pericardial sac over a one month period. The patient was apparently cured by this procedure.

Prognosis

The prognosis is usually good. Complete recovery in a matter of several days to some months is the rule.

Death may occur, however, from complicating factors. In all, four fatal cases have been reported in the literature.[4, 21, 22, 23] As noted, three of these died in cardiac tamponade, including the one fatal case (case 14) from this series. With increasing awareness of the disease, the mortality rate can be expected to rise. Presumably, cases have been misdiagnosed as myocardial infarction.

In this series, eight patients had recurrences, usually within the first year. Three or four attacks were not uncommon. One patient had 12 separate attacks over a period of four years (case 4).

General Discussion and a Review of the Literature

Idiopathic pericarditis tends to be a disease of young adults. Our average age of 31.5 years is somewhat lower, however, than that of previ-

ously reported series. Carmichael et al.[1] point out that cases do frequently occur in patients of the coronary age group. Thirty-six per cent of their cases were over 40 years of age, and 8% were over 60 years of age. In a series of 14 cases reported by Barnes and Burchell,[28] 57% were over 40 years of age, and all but two cases were over 30. The diagnosis of idiopathic pericarditis has probably been missed frequently in the older age group because of the similarity between the manifestations of pericarditis and coronary thrombosis, and the misconception that idiopathic pericarditis is a disease of young adults only.

Other authors agree that idiopathic pericarditis is predominantly a disease of males.[8, 28]

A somewhat higher incidence of upper respiratory infection associated with this disease than the 39% of cases found in this series has been reported previously.[1, 3]

An appreciation of the widespread distribution of pain in this disease (figure 2) is important and has been discussed in differential diagnosis. Other authors [1, 8, 32] have presented an essentially similar conclusion.

The physiology of pericardial pain is puzzling. Pain in the shoulders and neck is considered to be referred from that part of the parietal pericardium which overlies the diaphragm. It has been shown experimentally [33] that this area alone possesses nerve fibers sensitive to pain. The visceral layer is insensitive. The chest pain is thought to be due to involvement of the contiguous structures, such as pleura and mediastinum.[34]

Hill [35] has stressed the importance of abdominal pain in this disease. Powers, Read and Porter [36] in their series of 13 cases report five patients with significant abdominal pain. In one, an exploratory laparotomy was performed with negative findings. In another, the abdominal pain was severe enough for the diagnosis of perforated peptic ulcer to be made. In all these cases the pain later migrated to the chest, usually after a period of two or three days.

No correlation was noted between the degree of leukocytosis and the length or severity of disease. Carmichael et al.[1] found that the erythrocyte sedimentation rate proved to be a reliable measure of the clinical improvement of the patient. Our findings did not support this conclusion.

A typical electrocardiographic pattern has been described.[37] In the early stages of the disease, elevation of ST segments in Leads 1, 2, AVL and precordial chest leads develops; this may also occur in Leads 3 and AVF. The ST segment in AVR is characteristically depressed. After several days the ST segment usually becomes iso-electric, and the T wave decreases in amplitude and may become inverted. After a varying number of days or weeks, the T wave returns to normal. Reciprocal ST changes as seen in myocardial infarction do not occur, and Q waves do not develop. Should the pericardial reaction not be generalized, an atypical pattern will be observed.[38] Pathognomonic changes of pericarditis are seldom seen in a

single tracing, and serial electrocardiograms are usually necessary to confirm the diagnosis. The electrocardiographic changes seen in pericarditis of any cause are believed to be caused by involvement of the sub-epicardial layer of the myocardium, as shown by Vander Veer and Norris [39] in autopsy material, and by Burchell, Barnes and Mann [38] experimentally in dogs.

Carmichael et al.[1] noted cardiac enlargement in 50% of their cases; of these, three were stated to be due to effusion and 22 to cardiac dilatation. Levy and Patterson [3] reported similar findings. The criteria which these

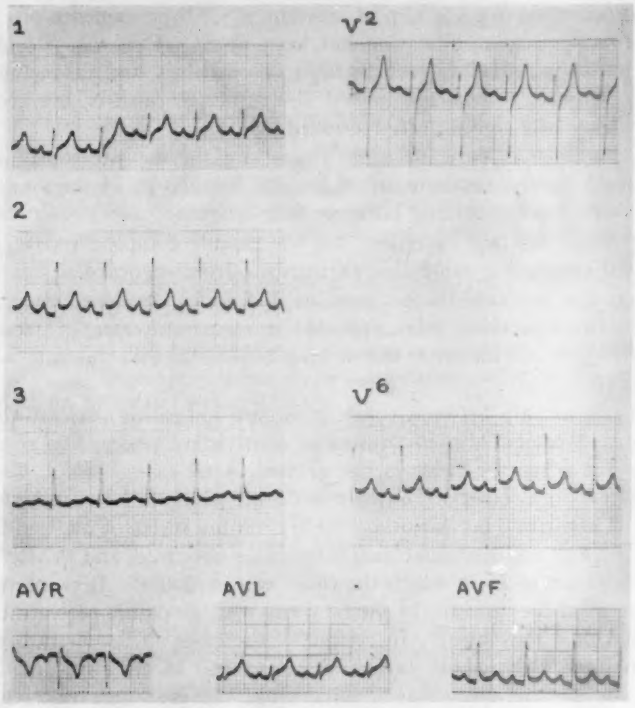

FIG. 4. A typical electrocardiographic pattern, as seen in case 14.

authors used for differentiating between dilatation and effusion are absence of signs of cardiac compression, lack of suppression of cardiac sounds, and normal voltages in the electrocardiogram. These criteria are debatable. It takes a considerable quantity of fluid to cause signs of cardiac compression when the effusion develops slowly, and the intensity of the heart sounds depends to a large extent on factors unrelated to pericardial effusion, such as the thickness of the chest wall and the state of the surrounding lung parenchyma.

Further, the radiologic differentiation of effusion from cardiac dilatation is difficult, and usually requires fluoroscopic examination and chest films in both supine and upright positions. With marked effusion the cardiac pulsations are diminished or absent, and the fluid is seen to shift, thereby altering the cardiac outline. Serial chest films may reveal transient enlargement of the cardiac silhouette, even though the cardiothoracic ratio does not exceed 1:2. This occurred in one of our cases (case 9).

Nor has a satisfactory mechanism been put forward to explain the concept of cardiac dilatation in idiopathic pericarditis. In those cases in the literature which have come to post mortem,[4, 21, 23, 24] no evidence of extensive myocarditis or cardiac dilatation has been noted. One case [22] had hypertension for 15 years before succumbing to pericarditis, and cardiac dilatation was present here. In uncomplicated idiopathic pericarditis, however, there is no evidence of a significantly increased load on the heart.

The findings at pericardicentesis substantiate the previously reported impression [4] that effusions occurring in the first 10 to 14 days are usually serous, while those occurring later are sero-sanguineous.

Levy and Patterson [3] suggest that the usually complete recovery is one way of differentiating idiopathic pericarditis from myocardial infarction.

Thirty-five per cent of the cases in this series developed recurrence of disease. Other authors have reported a recurrence rate of from 15 to 20%.[1, 3, 28, 32, 40] With better follow-up it is possible that this rate will prove to be higher.

The relationship between constrictive and idiopathic pericarditis is still in doubt. A review of the literature of constrictive pericarditis reveals that a history of a specific cause is not elicited in all cases. Paul, Castleman, and White,[41] in a series of 53 cases, had four which followed a history suggestive of idiopathic pericarditis. Kelly,[42] in his series of 39, had five such cases. Blalock and Burwell [43] had three cases out of 28, and White [44] earlier reported 10 out of 15 in which the cause was in doubt. It is interesting to speculate what the outcome of the fatal cases of idiopathic pericarditis might have been, had they lived. In certain of the cases in the literature a pericardium thickened in both layers was described at autopsy, and in some, fibroblastic proliferation was commencing. It is quite conceivable that constrictive pericarditis would have developed.

Summary

1. Twenty-three cases of idiopathic pericarditis are presented.

2. Death can occur in this disease. The one fatal case included in this series is the fourth to be described in the literature.

3. There is no specific therapy.

4. When there is evidence of cardiac tamponade, pericardicentesis may be important as a life-saving measure.

5. Although clear fluid is usually obtained in the pericardial effusion, bloody fluid may be present after the tenth day of disease.

ADDENDUM

Some of the cases from Queen Mary Veterans Hospital have been previously reported by Dr. S. F. Liu.[31]

SUMMARIO IN INTERLINGUA

Le crescente incidentia de pericarditis es notate. Vinti-tres casos es presentate. Le criterios de selection del casos es: presentia de dolor, un friction pericardial e/o un characteristic configuration electrocardiographic, e absentia de un demonstrabile causa specific de pericarditis.

Le morbo affice predominantemente juvene adultos mascule.

Pote occurrer un extense distribution de dolor, un alte incidentia de infection supero-respiratori, un malaise general, dyspnea, e molestias gastrointestinal. Le ruito de friction pericardial es per multo le plus importante signo. Febre, tachycardia, pleuritis, e pneumonitis pote esser presente. In tres del patientes del presente serie, pericardicenteses esseva executate. Moderate grados de leucocytosis e grados accelerate de sedimentation erythrocytic es frequente. Alterationes electrocardiographic es specialmente importante. Registrationes in serie pote servir a confirmar le diagnose.

Le litteratura de pericarditis idiopathic es passate in revista. Factores etiologic es discutite. Le diagnose debe sequer le exclusion meticulose de formas specific de pericarditis e de altere morbos que causa dolores thoracic e abdominal. Le diagnose differential de pericarditis idiopathic e infarcimento myocardial es specialmente importante. Nos opina que le diagnose de pericarditis idiopathic es frequentemente perdite in patientes de etates plus avantiate.

Il ha nulle therapia specific. Usualmente le prognose es bon. Recovramento complete pote esser expectate, ben que in le presente series 35% del casos disveloppava recurrentias.

Terminos mortal pote occurrer. Le presente serie include un caso de morte. Illo es le quarte describite in le litteratura. In le presentia de signos de tamponada cardiac, pericardicentese es possibilemente importante como mesura de salva-vita.

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RECENT ADVANCES IN THE LABORATORY DIAGNOSIS OF VIRUS INFECTIONS *

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INTRODUCTION

These are exciting days for the application of diagnostic methods to virus diseases, and the period is comparable to 40 or 50 years ago, when new bacteria were constantly being discovered. The etiology of many diseases was then clarified by the introduction of new methods for studying the morphology and cultural appearances of bacteria. In virology to-day, the introduction of new methods is having a similar effect, and we are witnessing advances without parallel in the history of the subject.

Until recently, the virologist was seldom in a position to offer to the practicing physician, facilities for prompt diagnosis. Tests for viruses involved the inoculation of fertile eggs and laboratory animals, in which the results of infection could not be recognized quickly, and so that further time-consuming examinations, such as histology, were usually needed. Considerable emphasis was placed on the necessity for serologic tests on acute and convalescent sera, with the demonstration of a significant increase in antibody.

Because of the realization that these classic diagnostic methods are of little value to the practicing physician, there is developing today a new concept in virus diagnosis. We are witnessing the establishment of clinical virus laboratories which employ methods capable of yielding presumptive evidence of infection while the patient is still acutely ill. Most large hospitals are now, or shortly should be, in a position to provide such facilities.

Foremost among these diagnostic methods are the new technics of tissue culture, which are rendering obsolete the time-honored methods of isolating viruses by inoculation of eggs and animals. Tissue cultures are particularly suited to this purpose, because they are sensitive to a wide range of viruses. The tissues and other materials can be readily obtained from human operation material or from monkeys, and many ingredients can be obtained commercially.

When viruses grow in the cells of tissue cultures, they produce a characteristic degeneration, or cytopathogenic change. Other lesions include the formation of giant cells, and nuclear or cytoplasmic inclusions.

The finding of such changes enables the virologist to offer a presumptive

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diagnosis based on recovery of virus from pathologic specimens. The responsibility of deciding whether this virus is the cause of the current illness falls on the attending physician. The isolation of diphtheria bacilli from a throat swab, for example, does not necessarily mean that the patient is suffering from acute diphtheria; he may only be a carrier.

In the same way, the isolation of polio virus from a stool of a sick child does not necessarily signify acute polio. However, in the presence of a consistent clinical picture, virus isolation affords strong presumptive proof of the accuracy of the clinical diagnosis.

Serologic tests on acute and convalescent sera still occupy an important place, especially in research studies and in the investigation of "new" diseases. A fourfold or greater increase in neutralizing or complement fixing antibody indicates that the virus has proliferated to a considerable extent, and is probably therefore responsible for the current illness.

Some Newer Technics in Virology

1. *Examination of Smears or Scrapings:* It is seldom practical to demonstrate the causal particles of virus diseases in smears prepared from lesions or exudates. Although these elementary bodies can be photographed by the electron microscope, this has never become a practical diagnostic procedure. Several particles have identical morphology, and differentiation is therefore impossible.

A few viruses are sufficiently large to be seen with the oil immersion lens in suitably stained films; for example, vaccinia, smallpox, molluscum, herpes zoster, herpes simplex, trachoma, and psittacosis. They appear, however, only as small dots, and this examination is of little value in differential diagnosis. Almost the only conditions where slide examinations are of practical value are trachoma and inclusion conjunctivitis, and the material examined must be a scraping of mucosal epithelium, not a smear of surface secretion.

Of more value is a test recently recommended by Blank and his colleagues in Philadelphia for the differential diagnosis of vesicular skin eruptions.[1] Scrapings are made from the base of the vesicles and are then stained. In herpes simplex, herpes zoster, and varicella, characteristic giant or Tzanck cells, with up to eight nuclei, can be found. These do not occur in vaccinia, smallpox, or other vesicular eruptions.

2. *The Use of Suckling Mice:* The introduction of the use of suckling mice by Dalldorf opened an important new chapter—the Coxsackie viruses.[2] These viruses can be separated into two groups on the basis of lesions produced in mice. Group A viruses cause myositis, whereas Group B viruses cause inflammatory changes in the dorsal fat pads and brain.

3. *Tissue Culture Technics:* Tissue cultures have been used in virology for at least 30 years, but only within the last few years has their practical

value in diagnosis become clearly established. Perhaps the most important reason is that the introduction of antibiotics has greatly simplified technical procedures. Previously, because of the frequent occurrence of laboratory contamination, it was necessary to conduct this work in special units. Elaborate precautions were taken to prevent contamination of the cultures. Although technicians wore caps, masks, gowns, and boots, infection of cultures still occurred.

Now that tissue culture media can be treated with antibiotics, contamination is very much less common. Infection is still a hazard, but no longer a deterrent, and relative amateurs have entered the tissue culture field and made significant contributions.

Another reason why tissue cultures have become more widely used is because technical methods have been greatly improved. Previously, only scanty growths of mammalian cells could be obtained. Now, with the improved methods, profuse confluent growths of human and monkey cells are commonplace.

Tissues now widely used in diagnostic work include epithelial cells from rabbit cornea, monkey kidney, human kidney, human amnion, or human embryo. A popular development is treatment with trypsin; this breaks up the tissue, and liberates epithelium which grows confluently in a single or "monolayer" sheet.

It is not always convenient to obtain fresh mammalian tissues, and this can be obviated by the use of HeLa carcinoma cells, which can be continuously cultivated in the laboratory.

In all of the types of culture mentioned, synthetic nutrient media prepared from chemicals, rather than nutrients containing various embryo extracts and animal sera, have proved suitable and give most reproducible results.

Another powerful stimulus to the widespread use of tissue cultures was the discovery by Enders, Weller, and Robbins in 1948 that polio virus produces microscopically recognizable changes in tissue cultures, the "cytopathogenic effect." [3] These changes are prevented by poliomyelitis antiserum. This new technic is available, therefore, not only for the isolation of virus, but for the measurement of serum antibody.

The essential novelty of this work was that a virus was shown to produce a microscopically visible token of infection, cell degeneration. Dulbecco and his colleagues now report that when polio and other viruses grow in a sheet of tissue culture cells covered with agar, they produce localized plaques or clearings of the tissue. For all practical purposes, these plaques are virus colonies.[4]

It is not unlikely that, before long, Dulbecco's technic may become part of diagnostic virology, for several viruses have distinctive plaques that enable differentiation to be made.

Poliomyelitis

Prior to the introduction of tissue cultures, the laboratory diagnosis of polio could be made only by the inoculation of monkeys. These develop paralysis between 7 and 21 days following inoculation, but histologic examination of the brain and cord is required to confirm the clinical diagnosis. Not infrequently, the animal does not sicken; it is then killed after 28 days, and a histologic examination is made. The diagnosis of polio by inoculation of monkeys is both slow and expensive; consequently, it has never been applied on a wide scale.

With the introduction of tissue cultures, however, laboratory diagnosis has suddenly come within the scope of public health and hospital laboratories; the method of choice is the attempted isolation of virus from pathologic specimens.[3, 5, 6]

Table 1

The Hospital for Sick Children, Toronto: Cases of "Poliomyelitis" Tested for Viruses in Stools by Inoculation of Monkeys, Suckling Mice, or Monkey Kidney Monolayer Cultures

	Paralytic Poliomyelitis	Non-Paralytic Poliomyelitis
Total	71	96
Positive poliomyelitis virus only	59 (83%)	11 (11.5%)
Positive poliomyelitis and Coxsackie A viruses	5 (7.1%)	3 (2.1%)
Positive poliomyelitis and Coxsackie B viruses	0	5 (5.2%)
Total positive poliomyelitis virus	64 (90%)	18 (18.8%)
Positive Coxsackie A viruses only	0	6 (6.3%)
Positive Coxsackie B viruses only	0	18 (8.8%)
Total positive Coxsackie A viruses	5 (7.1%)	8 (8.4%)
Total positive Coxsackie B viruses	0	23 (24.0%)
Negative poliomyelitis or Coxsackie viruses	7 (9.9%)	54 (56.4%)*

* Includes 11 "orphan" viruses.

Under favorable conditions, a diagnosis of the specific type of polio virus present can be made within three or four days of inoculation of tissue cultures.

The significance of a positive test for polio virus has to be considered in association with the clinical history, clinical features, and the findings in the cerebrospinal fluid. Isolation of virus from a throat swab is of greater significance than isolation from stool. Virus is present in the throat only for a few days, and its presence therefore suggests an acute infection. By contrast, virus is present in the stool for many weeks following infection; a positive test may therefore merely signify the convalescent stage of an earlier infection.

Nevertheless, the recovery of polio virus from a patient suffering from an acute illness clinically consistent with polio may be accepted as adequate laboratory confirmation.

The sensitivity of the newer types of tissue culture, for example monkey kidney cultures, to polio virus is considerable; in our laboratory, polio virus has been recovered from the stools of 90% of paralytic patients (table 1). Enders, using human tissues, has recovered virus from better than 90%.[7]

By contrast, in non-paralytic polio, virus can be recovered from only 20% to 50% of cases. This is because many alleged cases are infected with Coxsackie B, "orphan," mumps or other viruses, and not with polio (table 1).

The types of case of nervous illness in which physicians may be greatly helped by a report from the laboratory are as follows:

1. Paralysis of an isolated muscle group only, often the facial muscles.
2. Symmetrical paralysis suggestive of the Guillain-Barré syndrome.
3. Encephalitis occurring during times of polio.
4. Paralytic polio in infants, where diagnosis is notoriously difficult.
5. In persons who have received gamma globulin or polio vaccine as a prophylactic.

In this connection, the widespread employment of tissue cultures for laboratory diagnosis has had some unexpected results, and it is now realized that it is not possible to make a final diagnosis of paralytic polio by clinical means alone. Even if this diagnosis is confined to cases where paralysis is demonstrated on two occasions at 24 hour intervals, mistakes may still be made.

TABLE 2

Ontario: Poliomyelitis Vaccine Evaluation Study, 1955*

Final Clinical Diagnosis	Total Patients	Viruses Isolated from Stools		
		Poliomyelitis	"Orphan" or Coxsackie	Negative
Paralytic poliomyelitis	6	2	0	4
Nonparalytic poliomyelitis	43	5	19	19
	49	7	19	23

* Includes some results kindly furnished by Dr. N. A. Labzoffsky, Ontario Department of Health, Toronto.

This problem came to light when specimens from paralyzed patients in the gamma globulin trial of Hammon, 1951 and 1952, were tested by laboratory methods, for no polio infection could be demonstrated in several typical cases of paralytic poliomyelitis.[8]

Difficulties in diagnosis were even more prominent in the 1954 trials of "Salk type" vaccine. In the states of New York and Massachusetts, for example, there were epidemics of an illness characterized by lesser degrees of paralysis. Polio virus was not isolated from these cases; but many specimens yielded so-called "orphan" viruses.[9]

We have had a similar experience in Ontario, where vaccine was extensively used in 1955 (see table 2).

6. Non-paralytic poliomyelitis must always be investigated by laboratory methods.

We have recently investigated 96 cases of this syndrome. Only 18 (18.8%) of the patients were found to be infected with polio virus. Many of the others were infected with Coxsackie Group B virus, or "orphan" viruses (table 1).

To conclude my remarks on poliomyelitis, I have stressed the value of isolation tests on pathologic specimens for prompt laboratory diagnosis. However, in special research studies, and in those cases where the results of tests for excretion of virus conflict with the clinical findings, it is desirable to carry out serologic tests on acute and convalescent phase blood. Both the complement fixation and virus neutralization tests may be used. The virus neutralization test has been more widely employed, and from the point of view of diagnosis, is, I think, more informative. These tests can be carried out in tissue cultures. In approximately 50% of cases of poliomyelitis, a significant increase in antibody in the convalescent phase serum can be detected, provided the first serum has been taken early. In the other cases, high levels of antibody to the infecting type of virus are found in both samples.

Complement fixing antibody persists for a relatively short period following infection, and it has been suggested that a positive test, even on a single sample, affords suggestive evidence of acute polio.[10]

Coxsackie Infections

Coxsackie viruses are named for the town in New York, where suckling mouse pathogenic viruses were first isolated by Dalldorf and Sickles in 1947. In that year, many parts of North America were visited by febrile illness, diagnosed as influenza, "summer grippe," "non-paralytic poliomyelitis," or epidemic myalgia.

It now seems unlikely that the original Dalldorf and Sickles viruses were associated with this particular epidemic. Nevertheless, their work provided a tremendous stimulus to virus diagnosis. Their methods of inoculation of specimens into suckling mice were widely adopted. Soon, it became evident that there is no such single entity as "Coxsackie virus," rather, there are two different groups, A and B, which can be differentiated by the pathologic changes produced in suckling mice of 24 hours of age. By virus neutralization tests, Dalldorf has separated Group A strains into 19 types and B viruses into 5 types. Group B strains all grow in tissue cultures and this greatly facilitates laboratory diagnosis.[2]

Group A viruses cause herpangina, an ulcerative condition of the pharynx first described by Zahorsky. The work of Huebner and his associates in Washington, a few years ago, showed that herpangina is a specific entity with characteristic clinical features, and is caused by Group A Coxsackie viruses.[11]

The disease occurs characteristically in the summer and fall, mainly in children. The presenting symptoms are often headache and vomiting, and

"punched-out" ulcers rapidly develop on the tonsil and posterior pharyngeal wall. The ulcers are discrete, and seldom number more than about a dozen. Lesions do not occur on the gums or lips, as they do in herpetic stomatitis.

Laboratory diagnosis is made by isolation of Coxsackie A viruses from throat swab or stool in suckling mice. Virus neutralizing antibody develops in convalescence, and can be detected by inoculation of mice with serum-virus mixtures. Only a few strains of Group A virus grow in tissue cultures, which cannot therefore replace mice for diagnosis.[11]

Pleurodynia and Aseptic Meningitis

Epidemic pleurodynia was widely prevalent in 1931 in Scandinavia, and Sylvest, spending a holiday on the Island of Bornholm, studied the disease in the islanders: hence the name, Bornholm disease.[12] Many outbreaks have occurred in North America.

It is now customary to refer to Sylvest's disease as "Bornholm disease," a term which includes at least four manifestations: epidemic pleurodynia; epidemic myalgia; aseptic meningitis; and cases of minor or abortive illness.

Studies on the etiology of pleurodynia began in 1947, when strains of Coxsackie virus Group B 1 were isolated in Massachusetts. Other strains were isolated in 1948 in New England, and in 1951 in Washington and Texas. Numerous isolations have also been made in Sweden and Britain (chiefly B 3 strains).

Evidence of the etiologic rôle of Group B strains is as follows: (1) frequent recovery from cases; (2) demonstration of antibody increase in convalescence; (3) rare occurrence in normal persons.

Laboratory diagnosis of pleurodynia is made by inoculation of throat washings or stool in suckling mice or preferably in tissue cultures; a virus neutralization test can be performed on paired sera.

Of particular interest has been the unfolding of the evidence that Coxsackie B viruses are a not uncommon cause of aseptic meningitis.[2, 13, 14] Twenty years ago, Sylvest described patients suffering from epidemic pleurodynia, who also had aseptic meningitis. Subsequently, many others have recorded meningitis as a complication of epidemic pleurodynia or myalgia. Furthermore, various workers, especially in Sweden, have reported the coexistence of epidemics of Bornholm disease and aseptic meningitis.[13] The relationship is so intimate that common etiology of the two conditions can be assumed.

Direct evidence for the etiologic rôle of Coxsackie B viruses is also available. From 1947 onwards, many workers have isolated Group B strains from the stools of cases of "non-paralytic poliomyelitis" or aseptic meningitis. In practically all of the patients tested, significant increases in antibody have developed. Tests for the presence of polio have proved negative.[14]

Furthermore, several workers have isolated Coxsackie B viruses directly from the cerebrospinal fluid.[2] Over 20 such isolations have been made in Sweden, South Africa, Canada, and the United States. We have isolated five strains (table 3).

There is no longer any doubt that Coxsackie B virus is a fairly common cause of aseptic meningitis. Studies carried out in Sweden, and our own studies, suggest that about 20% of cases diagnosed clinically as "non-paralytic poliomyelitis" are in fact examples of Coxsackie B meningitis.[13, 14, 15]

TABLE 3

Aseptic Meningitis: CSF Samples Inoculated in Monkey Kidney Cultures

Total CSF Samples	60
Coxsackie B isolated	5*†
"Orphan" isolated	3†
Negative	52

* Types: B2, one strain; B4, four strains.
† Similar viruses excreted in stools.

We have studied eighteen such cases with considerable care, but analysis reveals no characteristic clinical features. The average cerebro-spinal fluid cell count, on admission, was 180 per cu. mm. and the sugar was normal.

"Orphan" Viruses

The widespread use of tissue cultures for the investigation of the etiology of cases of poliomyelitis has led to the discovery of a new group of viruses called "orphan" viruses, or "enteric cytopathogenic human orphan viruses," abbreviated as "echo" viruses.[16] These viruses have been isolated most frequently from the stools of patients with aseptic meningitis. They can be accepted as the cause of illness in man, for we have isolated three strains directly from the cerebrospinal fluid (table 3). Much work yet remains to be done on the virology of these agents, which are not related to polio or Coxsackie viruses, and probably represent several new groups, some pathogenic, some harmless.

"R. I. 67" and "APC Viruses"

A whole host of respiratory illnesses resemble each other clinically, but have different names: febrile catarrh, acute respiratory disease or ARD, feverish colds" and even "flu," or "virus" pneumonia.

The value of tissue cultures for investigating the etiology of disease has been beautifully illustrated by the studies of Huebner, Hilleman, and their associates,[17, 18] who have shown that at least some of these illnesses are caused by members of the group of viruses known as the adenoidal-pharyngeal-conjunctival or APC viruses. The viruses grow best in HeLa cell cultures and produce characteristic degenerative changes.

Our own experience relates chiefly to another APC virus infection: pharyngeal-conjunctival fever.[19] My colleague, H. L. Ormsby, in the summer of 1955, studied a severe outbreak traced to use of a swimming pool in Toronto.[20, 21] The cases showed a severe follicular conjunctivitis, usually bilateral, with preauricular adenitis and some upper respiratory symptoms. Whole families were attacked. Some patients developed corneal opacities. APC viruses belonging to type 3 were isolated in HeLa cells.

Recent studies suggest that at least some examples of the well established eye disease known as epidemic keratoconjunctivitis (EKC) are caused by these APC viruses.

Acute Laryngotracheobronchitis

This is an acute respiratory infection of children, occurring mainly in the winter and presenting as a medical emergency, for some cases develop "croup" and urgently require tracheotomy.

It has been suggested for many years by Rabe and others that one form of this disease is caused by a virus,[22] for there is no specific bacteriology; epidemiologically these infections are often connected with common colds, and there is usually a leukopenia.

My associates and I have recently investigated the possibility of a virus etiology. Specimens of post-nasal washings, or washings from tracheotomy tubes have been collected, and extensive bacteriologic and virologic tests have been carried out. The results were negative at first, but later we obtained suggestive evidence of a virus in tissue cultures of human lung.

More recently, HeLa cell cultures and human amnion cultures have given better results. Specimens from seven of 14 cases have yielded cytopathogenic agents, presumably viruses. Serologic tests have been carried out in some patients, and have shown a definite increase in antibody.

The virus has not yet been identified, but it does not appear to be a member of the APC group, influenza, herpes, or any other common virus.

Exanthemata and Vesicular Skin Eruptions

Most physicians have encountered problems in the differential diagnosis of patients covered with a profuse vesicular eruption. The term Kaposi's varicelliform eruption is applied to these illnesses, and there is often a history of atopic dermatitis. "Kaposi's eruption" is a general term, and covers infections caused by the viruses of herpes simplex, vaccinia, zoster, and varicella.[23] Another diagnostic problem concerns the recently vaccinated person who develops vesicular lesions elsewhere on the body.

First of all, a scraping should be made from the base of the vesicles on slides or coverslips, and stained for giant cells as recommended by Blank et al.[1] In herpes simplex, herpes zoster, and varicella, large multinucleated giant cells will be seen, with typical intranuclear inclusion bodies. These cells are not found in vaccinia or smallpox.

Secondly, tissue cultures should be inoculated with vesicle fluid. Cultures of rabbit corneal epithelium are very suitable.[23, 24] Herpes simplex virus quickly produces cytopathogenic changes in these cultures, giant cells are formed, and numerous nuclear inclusion bodies can be found. Such changes develop within 8 to 10 hours. The viruses of zoster and varicella do not produce changes in rabbit corneal tissue cultures, but may do so in human epithelium. Vaccinia virus produces characteristic degenerative changes, but intracytoplasmic inclusions not nuclear inclusions are present.

Summary

The introduction of the newer methods of tissue culture has brought the laboratory diagnosis of many virus infections within the reach of public health and hospital laboratories. It is now possible in many virus infections to offer to the physician a presumptive report, based on isolation of virus from pathologic specimens, at a time when the patient is still acutely ill.

This paper has discussed recent advances in the laboratory diagnosis of poliomyelitis; Coxsackie infections such as herpangina, pleurodynia, and aseptic meningitis; "orphan" virus infections; APC virus infections; acute laryngotracheobronchitis; and vesicular skin eruptions.

Acknowledgments

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Summario in Interlingua

Le introduction de nove methodos virologic, specialmente de methodos de histocultura, resulta in progressos sin parallela in le historia de iste subjecto. Usque recentemente le virologo non habeva ulle medios de prompte diagnose a offerer al medico practic. Sed hodie le virologo pote establir un diagnose presumptive super le base del viruses identificate in specimens pathologic per medio de inoculationes in histoculturas.

Le presente articulo discute brevemente certe altere progressos recente in le campo del diagnose laboratorial. Le valor del examine de grattages de pelle vesicular es sublineate. In appropriatemente colate preparatos de herpes simplice, zoster, o varicella, multinucleate cellulas gigante (Tzanck) pote esser trovate. Istos non occurre in vaccinia, variola, o altere eruptiones vesicular. Le uso de inoculationes de muses lactante in le diagnose de infectiones a Coxsackie es etiam mentionate.

Le plus recente typos de histocultura es describite, e le rationes es explicate pro que iste technica de diagnose laboratorial esseva exploitate solmente a un tempore satis recente. Es signalate le valor del diagnose laboratorial in casos de poliomyelitis. Virus de poliomyelitis ha essite isolate in solmente 20% del casos de "poliomyelitis non-paralytic" que—secundo le experientia del autor—es un syndrome causate tanto frequentemente per virus Coxsackie B como per virus de poliomyelitis. Es mentionate le interesse del occurrentia de morbos paralytic que es apparentemente non causate per virus poliomyelitic. Iste facto es responsabile pro certe problemas que esseva incontrate in recente essayos con vaccino de poliomyelitis in le Statos Unite

e etiam in Ontario. Le uso de technicas laboratorial in le diagnose de infectiones a Coxsackie es describite, per exemplo in casos de herpangina, pleurodynia, e meningitis aseptic. Le autor reporta le constatationes clinic e laboratorial in 18 casos de meningitis aseptic causate per le virus Coxsackie B. Cinque de iste patientes excerneva virus Coxsackie B in le fluido cerebrospinal.

Le articulo describe experientias con viruses del typos "orphan" e "APC." Duo racias de viruses del prime de iste typos esseva trovate in le fluido cerebrospinal de casos de meningitis aseptic. Finalmente, un virus que pare esser "nove" esseva trovate in septe casos de acute laryngotracheobronchitis.

Le objectivo del presente articulo es signalar al beneficio del medico practic le facto que le laboratorio virusal pote esser de adjuta in le diagnose de multe morbos virusal e que illo pote facer lo satis promptement.

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ACUTE RHEUMATIC FEVER IN A LARGE SOUTHERN HOSPITAL OVER THE FIVE YEAR PERIOD 1950 THROUGH 1954 *

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Medical literature contains little information regarding the incidence of acute rheumatic fever in the central southern portion of the United States, although in the past there have been reports from other sections.[1, 2, 3] The purpose of this paper is to report this disease as seen on the wards of Confederate Memorial Medical Center, of Shreveport, Louisiana, a 1,000 bed general hospital for the care of indigent citizens of Louisiana. The drawing area of this hospital is primarily the northern part of the state.

Admissions: During the five year period from January 1, 1950, through December 31, 1954, there were 105,476 admissions to the hospital wards. During the same period the yearly admission rate for the combined Pediatric and Internal Medicine Wards varied from 24% to 30% of the total for the hospital, averaging 26%. The total number of admissions recorded as possible or proved acute rheumatic fever was 343. By fulfilling the criteria for diagnosing acute rheumatic fever established by the Joint Report of the British Medical Research Council and the American Heart Association,[3] this diagnosis was felt to be established justifiably in 162 admissions. This comprised a five year mean of 0.59% of all admissions to the combined Pediatric and Internal Medicine Wards (table 1). In this group of admissions were 149 different patients. Several of these had repeated admissions for recurrent acute rheumatic fever. The statistics, however, are for total admissions (162), and not for the true case load (149). Since this is such a small number of cases for reporting statistics, and since only 20 white patients were involved, the report has incorporated both races into its calculations, except where indicated below.

Manifestations: Table 2 shows the incidence of major manifestations. A point of interest is the much greater frequency of carditis that was found in the female, giving greater than a two-to-one incidence over the male. Table 3 shows the incidence of minor manifestations.

Race and Sex: Figure 1 gives statistics on incidence by race. Only 12% of the 162 patients were white, the rest Negro. Figure 2 shows sex inci-

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dence. Of the 20 whites, 12 were male and eight female, revealing a female-to-male ratio of 1:1.5. Of the 142 Negroes, 53 (37.3%) were male, and 89 (62.7%) female, giving a female-to-male ratio of 1.7:1.

Age: Figure 3 gives incidence by age groups. It is seen that the greatest incidence is in the 10-through-14 year group, followed in turn by the five-

TABLE 1

Relationship of Incidence of Acute Rheumatic Fever to Medical Admissions in Two Louisiana Hospitals

Confederate Memorial (Shreveport)			Charity (New Orleans)		
Year	Rheumatic Fever	Medical Admissions*	Year	Rheumatic Fever	Medical Admissions*
1950†	25	4,840	1049–50‡	70	11,991
1951	31	5,174	1950–51	85	11,604
1952	37	6,010	1951–52	68	11,994
1953	30	5,547	1952–53	83	12,656
1954	39	5,951	1953–54	76	12,910
Total	162	27,522		382	61,155
RF:MA	1:170	(0.59%)		1:160	(0.62%)

* Admissions to the Medicine and Pediatric Wards.
† Calendar year.
‡ Fiscal year—July 1 of one year through June 30 of the following year.

through-nine, then the 15-through-19 groups. Table 4 gives age ranges and mean ages by sex and episode. Of the 162 episodes of acute rheumatic fever, 92 (56.8%) were initial, and 70 (43.2%) recurrent. The mean age for initial episodes was 13.5 years; for recurrent episodes, 15 years; for all episodes, 14 years.

TABLE 2

Incidence of Major Manifestations, 162 Admissions, 1950–1954

Manifestations	White		Negro		Combined		Total	Per Cent
	Male	Female	Male	Female	Male	Female		
Carditis	5	7	24	55	29	61	91	56.2
Polyarthritis	9	4	37	53	46	57	103	63.6
Chorea	1	2	4	8	5	10	15	9.3
Subcutaneous nodules	0	0	2	3	2	3	5	3.1
Erythema marginatum	0	0	1	0	1	0	1	0.6

Monthly Incidence: Figure 4 reveals a fairly steady number of cases occurring in each of the 12 months over the entire five-year period, the curve giving one maximum in March and a second in November.

Deaths: Of the 162 admissions (149 cases), there were nine deaths (admission incidence of 5.5%; case incidence of 6%). These were all due

TABLE 3

Incidence of Minor Manifestations, 162 Admissions, 1950–1954

Manifestations	White		Negro		Combined		Total	Per Cent
	Male	Female	Male	Female	Male	Female		
Fever	12	7	48	76	60	83	143	88.3
Elevated erythrocyte sedimentation rate	10	7	48	74	58	81	139	85.8
Prior infection	7	4	26	54	33	58	91	56.2
Increased P-R interval	2	1	12	14	14	15	29	17.9
Positive past history	5	3	18	38	23	41	64	39.5

to intractable cardiac decompensation, and consisted of seven Negro females, with an age range of 8 to 12, mean age of 9.9; a 17 year old Negro male and a 20 year old white male, revealing a female-to-male death ratio of 3.5 : 1.

DISCUSSION

Introduction: Whereas most surveys studying the problem of rheumatic disease concern themselves with limited age groups—for example, limiting cases to those not older than 13 years,[4] or 20 years [5]—this study includes all cases diagnosed as acute rheumatic fever, regardless of age. Many reports also include cases in an inactive state. These factors make comparison difficult and conclusions subject to error. However, a recent report by Bruce [1]

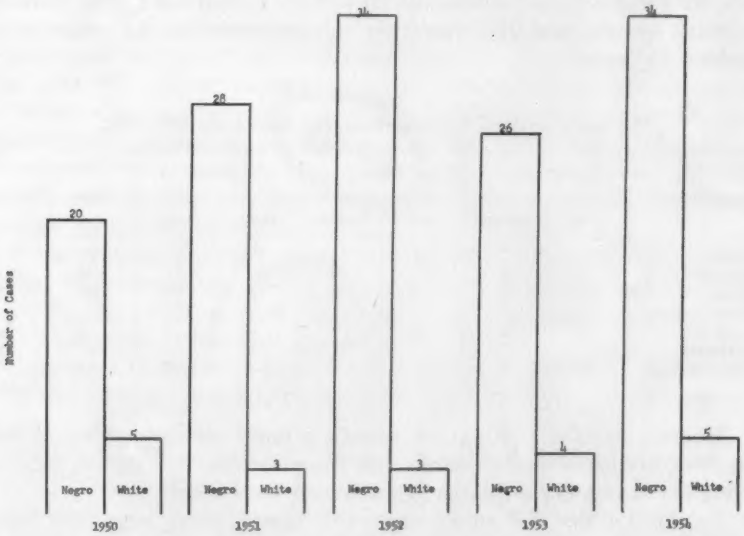

FIG. 1. Race incidence.

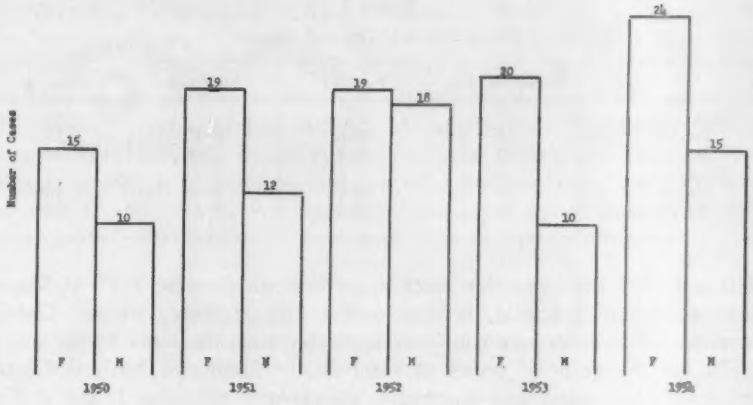

FIG. 2. Sex incidence.

from the State of Washington consisted of a survey limited to acute rheumatic fever, as did another recent report by the British Medical Research Council and the American Heart Association.[3]

Admissions: In 1935 Seegal et al.[6] reported on the incidence of rheumatic fever throughout the United States as recorded in major hospitals. Between

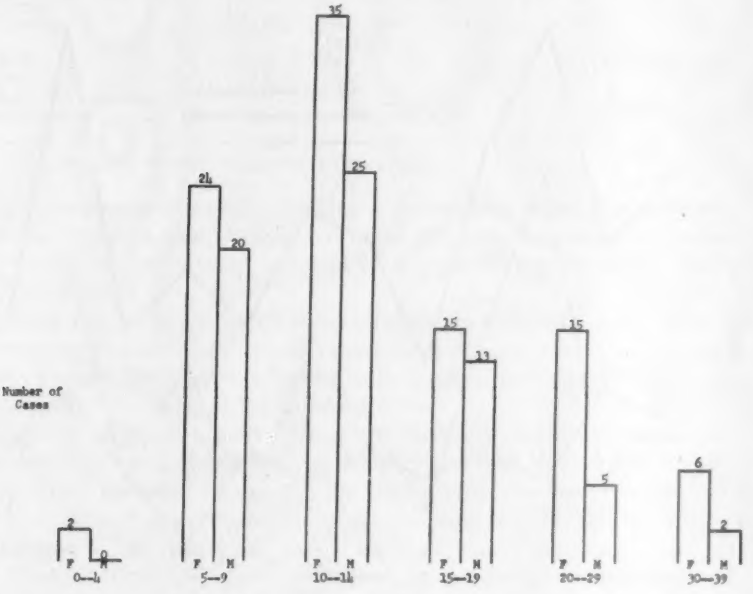

FIG. 3. Incidence by age group.

TABLE 4

Age Incidence by Sex and Episode

	Number of Cases	Per Cent	Age Range	Mean Age
Male				
Initial	38	58.5	6–25	12
Recurrent	27	41.5	6–36	15
Female				
Initial	54	55.7	3–39	14
Recurrent	43	44.3	5–36	15

1910 and 1925 the admission rates to medical wards were 1:70 at Massachusetts General Hospital, Boston, and 1:161 at New Orleans' Charity Hospital. The latter rate compares favorably with the more recent one of 1:170 for the authors' series at Confederate Memorial Medical Center, Shreveport, Louisiana, and remarkably closely with the value 1:160 at New Orleans' Charity Hospital for the period July 1, 1949, through June 30, 1954, as shown in table 1. This implies, as previously pointed out in the literature, the apparently milder course that acute rheumatic fever runs in warmer climates. The lack of remarkably greater occurrence during the winter and spring months may be associated with the generally milder climate in this part of the country, which had a mean temperature of 66.5° F., and a mean rainfall of 41.95 inches during the period studied.

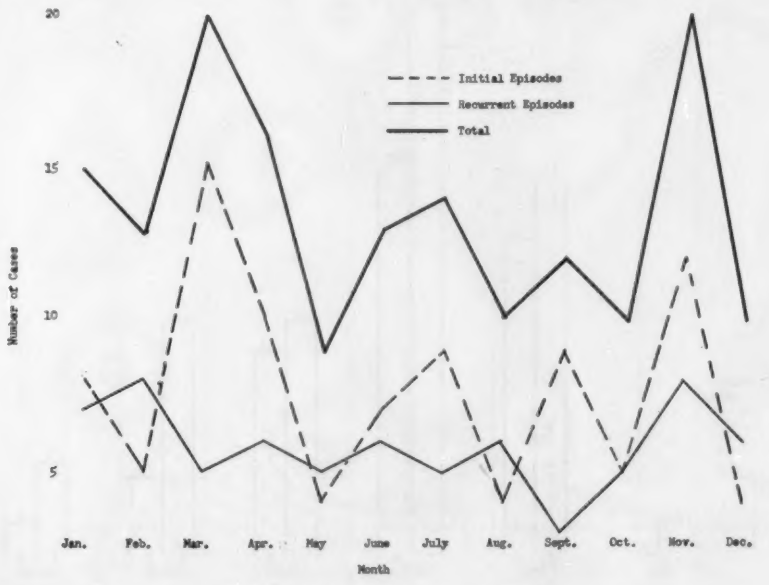

FIG. 4. Monthly incidence of acute rheumatic fever.

Race: The incidence of white admissions in this series was only 12%. This low figure was in part determined by the difference in admissions between the white and Negro races, the latter comprising from 71% to 75% of total hospital admissions during the period studied. Other series give white-to-Negro ratios of 113:20,[7] 82:14,[8] and 142:83.[9] This tremendous variation is undoubtedly due to population ratios in various localities in this country, as well as to available bed space for the two races, and to relative economic levels. A rate corrected for admissions would give about 25% white incidence. This is about twice as high as was found in this survey.

TABLE 5

Major Manifestations—Comparison of Various Series

	Lieber and Holoubek	Bruce[1]	Joos and Katsampes[2]	Bland and Jones[5]	United Kingdom-United States[3]
Period studied	1950–54	1951–52	1949–50	1921–51	1951–52
Number of cases	162	386	52 (with active disease)	1,000	497
Age range	3–39	Preschool to over 35	4–24	Under 21	Under 16
Mean age	14	17	11±	8 (original status)	10
Male	65	About equal	31	291	259
Female	97		21	709	238
Major manifestations (per cent)					
Carditis	56.2%	38 ("carditis")	44.5*	63.5	76.4
Arthritis	63.6	76.1	72.2*	41.0	43.3
Chorea	9.3	3.5	19.4*	51.8	10.9
Subcutaneous nodules	3.1	6.5	—	8.8	14.3
Erythema marginatum	0.6	9.5("rash")	—	7.1	5.8

* Incidence for 36 cases during the initial episode.

The lower economic level for the Negro in this area, allowing greater crowding and exposure, poor health, and other factors associated with increasing the Group A streptococcal infection in a population, probably accounts for the difference.

Sex: The literature shows differences in sex incidence, some series presenting more male cases [1, 3] and others more female cases.[4, 7] The present series reveals 59.9% of admissions to be females, and 40.1% males, giving an over-all ratio of 1.5:1 for females to males.

Age: Two recent reports [1, 2] deal with incidence of active rheumatic fever, regardless of age. Table 5 gives comparisons with the present series. It is seen that the mean age for the Louisiana Series lies between that for the New York and Washington State series, being 14, 11 and 17 years, respectively.

Manifestations: As shown in table 5, major manifestations occurred in the following order of diminishing frequency: arthritis, carditis, chorea,

subcutaneous nodules, and erythema marginatum. The 63.6% incidence of arthritis compares quite favorably with the mean incidence of the other series of 58%, as does the 56.2% incidence of carditis compare with a 56% mean for the other series. The low incidence of specific rash is most likely due to the difficulty in diagnosing evanescent macular and serpiginous rashes in darkly pigmented skin.

Summary

The incidence of acute rheumatic fever is presented as observed in a large southern (Louisiana) hospital for indigents, covering the five year period January 1, 1950, through December 31, 1954.

Statistics on age, sex and race incidence, and criteria for diagnosis, are compared with other recent surveys.

Summario in Interlingua

Esseva executate un studio del combinate admissiones al departimentos pediatric e de medicina interne del "Confederate Memorial Medical Center" pro le annos 1950 a 1954. Le Centro es un hospital general de 1.000 lectos pro patientes indigente a Shreveport in Louisiana. Le numero total del admissiones esseva 27.522. Le diagnose de acute febre rheumatic esseva establite in 162 casos (0,59%). Le proportion de febre rheumatic esseva 1 caso inter 170 admissiones. Iste proportion es nettemente comparabile al proportion de 1 a 160 constatate pro le mesme periodo al Hospital Charitative de New Orleans. Durante le periodo ab 1910 a 1925 le correspondente proportion al Hospital Charitative de New Orleans esseva 1 a 161, e al Hospital General de Massachusetts illo esseva 1 a 170.

Le total de 162 diagnoses de acute febre rheumatic includeva 20 patientes blanc e 142 patientes negre. Nos opina que le alte incidentia de patientes negre esseva le effecto del relativemente basse nivello economic del population negre in iste area con le consequentia de plus restringite conditiones domiciliari, un hygiene inferior, e plus alte grados de exposition a infectiones per streptococcos del gruppo A. Le serie total includeva 65 masculos e 97 femininas. Le etates variava inter tres e 39 annos. Le etate median esseva 14 annos. Le plus alte incidentia occurreva inter le quinte e le dece-quarte anno del vita. In 92 casos il se tractava de episodios initial; in 70 casos il se tractava de recurrentias de febre rheumatic. Le plus alte incidentia mensual occurreva in martio e novembre.

Le serie includeva nove mortes, octo in negros, un inter le blancos. Omne le mortes resultava de intractabile discompensation cardiac. Le incidentia de major manifestationes de febre rheumatic esseva arthritis (63,6%), carditis (56,25%), chorea (9,3%), nodulos subcutanee (3,1%), e erythema marginate (0,6%).

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CASE REPORTS

IDIOPATHIC ORGANO-AXIAL VOLVULUS OF THE STOMACH: CASE REPORT *

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In 1866 there appeared in the literature for the first time a report of recurrent gastric volvulus; Berti [1] described a forward, upward rotation of the stomach, traversing an arc of 180 degrees. Since that time an additional 100 cases have been documented.

Gastric volvulus has been variously classified. Payer [2] divides this condition into two groups: idiopathic and secondary. Other authors utilize an anatomic framework of reference; the nature of the mesentery and character of rotation determine the nomenclature. Thus Borchardt [3] describes a supracolic and infracolic type, depending upon whether the colon assumes an anterior or posterior position in relationship to the body of the stomach.

The etiology of gastric volvulus cannot be clearly defined. However, several factors are generally recognized as contributory. These may be classified as follows:

I. Intrinsic
   A. Congenital
      1. Abnormalities of the mesentery
         a. Failure of fixation of the greater omentum to the transverse colon
         b. Congenital elongation of the gastrocolic ligament
      2. Eventration of the diaphragm
      3. Hourglass stomach
      4. Defects of the left lobe of the liver
   B. Acquired
      1. Left diaphragmatic hernia
      2. Tumors
         a. Gastric
         b. Perigastric
      3. Displacement of adjacent organs
      4. Inflammatory processes in the vicinity of the stomach

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II. Extrinsic
  A. Somatic
    1. Extra-abdominal pressure
      a. Girdles, trauma, et cetera
    2. Gastric distention
      a. Food
      b. Aerophagy
  B. Psychic

Whatever the contributory causes, it appears that the mechanism in the production of gastric volvulus is based on the relationship between the greater curvature of the stomach and the transverse colon, since the movements of these two structures are more or less coördinated by their loose attachment via the gastrocolic ligament.[4] As the greater curvature rotates upward, the transverse colon is pulled with it—the greater the rotation, the more pronounced the ascent of the transverse colon. The transverse colon may finally rest above the level of the stomach, should the latter move 180 degrees around its axis. Conversely, if the transverse colon is forced into a supragastric position by virtue of aerocolon, congenital anomalies, et cetera, its displacement may conceivably initiate gastric volvulus.

Regardless of the factors enumerated, in all cases reported some anatomic anomalies were present, especially the failure of fusion of the greater omentum with the transverse colon; this, naturally, renders the stomach susceptible to various displacements.

The clinical picture of gastric volvulus varies. There may be a paucity or even complete absence of symptoms.

Usually there is abdominal distress, which may be mild to severe, acute, intermittent or constant, depending on the degree of rotation. In those types in which acute upper abdominal distress occurs, Borchardt's triad may be helpful in the differential diagnosis. This syndrome consists of strong and generally fruitless efforts to vomit, circumscribed epigastric pain, and resistance to the passage of a stomach tube.[1] If emesis is productive, there is usually absence of bile,[6] presumably due to complete obstruction of the pars pylorica. To assist in establishing a diagnosis, some clinicians endeavor to pass a sound. However, because of the danger of perforation,[5] a barium swallow study is preferable.

When rotation approaches 180 degrees, obstruction or strangulation of blood supply becomes imminent. Beyond axial rotation, patients usually present the clinical picture of an acute abdominal emergency, with signs of complete obstruction and progressive strangulation. Death may ensue unless relief is immediately afforded. Occasionally spontaneous reduction occurs.

The treatment of gastric volvulus is surgical except in poor-risk patients and those with infrequent mild attacks easily controlled by brief intubation and supportive measures.

Case Report

A 37 year old married Caucasian female who enjoyed prior good health was admitted to the Cedars of Lebanon Hospital on August 1, 1955, with a history of having suffered from recurrent upper gastric distress. In view of the contemplated treatment her past history was especially significant: early in 1953 she had suffered

from an attack of acute abdominal pain for which an appendectomy was performed; reference to the records revealed that the appendix was normal.

On October 10, 1955, the patient developed severe mid-upper gastric cramping pain two hours following the ingestion of a chicken dinner. The pain remained localized, returned in waves and was severe enough to cause her to writhe and double up. Shortly thereafter she vomited her recently ingested food; the vomitus was free of bile. One and a half hours later she developed shaking chills and became semistuporous. At this time examination revealed decided mid-upper abdominal tenderness; rebound tenderness was absent. The patient appeared markedly dehydrated and, although coherent and coöperative, was somewhat lethargic. Her blood pressure was 120/80 mm. of Hg and her pulse was 90 per minute. There were

FIG. 1. Upper gastrointestinal series demonstrating volvulus.

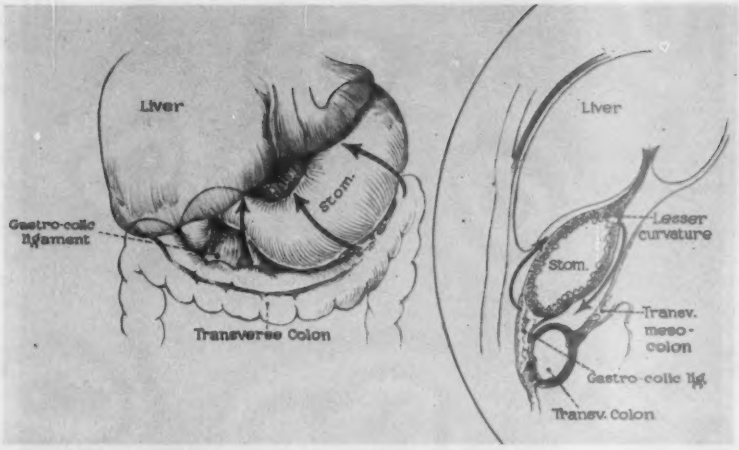

FIG. 2. Organo-axial volvulus. Stomach in normal position. Arrow indicates its direction of rotation.

no other significant physical findings. Laboratory results were as follows: white blood count, 14,500, with 81% neutrophils (segmented, 72%, and stabs, 9%), 1% eosinophils, 15% lymphocytes, and 4% monocytes; red blood count, 4,950,000, with 89% hemoglobin (14.3 gm.); blood amylase, 110 units; carbon dioxide combining power, 14 vol.%; urinalysis: specific gravity of 1.035, 2 plus albumin, 4 plus glucose,

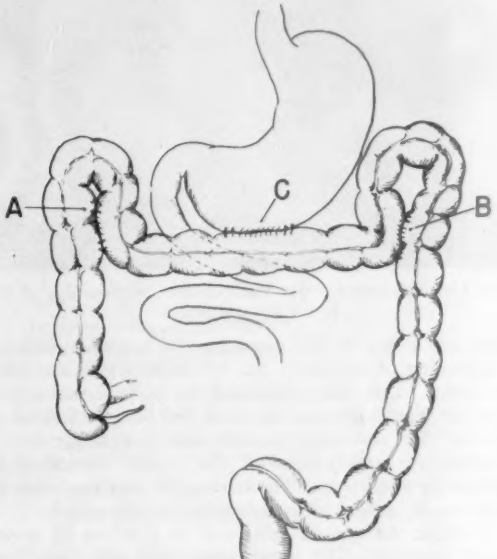

FIG. 3. Artist's drawing of surgical repair. (From Lichtenstein and Lasky: Gastric volvulus, California Medicine; to be published.)

FIG. 4. This film demonstrates the postoperative relationships of the stomach to the plicated colon.

a trace of acetone, and a pH of 5.5; serology was negative; blood sugar was 181 mg.% during the evening of admission but fell to 99 mg.% the following morning, at which time the urine sugar was 1 plus and the acetone was negative. Curiously enough, several weeks later a glucose tolerance test was performed and found to be within normal limits. The sedimentation rate was 23 mm. per hour.

The symptoms having largely subsided, the patient insisted on leaving the hospital, 48 hours following admission. The etiology of this condition was obscure, but some type of acute upper abdominal catastrophe was presumed.

Following discharge the patient submitted to a series of x-rays. The cholecystography proved negative. The upper gastrointestinal films, however, revealed a gastric volvulus. When the patient was shifted from the P.A. to the lateral view with pedicle formation at the duodenum there was noted a complete shifting of the curvatures of the stomach (figure 1). The volvulus was easily reduced by returning

the patient to a supine position. X-ray several months later confirmed these observations. Barium enema failed to demonstrate either intrinsic or extrinsic lesion of the colon, nor was there any evidence of general or anatomic variations; during fluoroscopy barium freely outlined the entire colon.

Because of recurrent episodes of upper abdominal distress, and in view of the danger of obstruction and strangulation, the patient agreed to surgical correction of her gastric volvulus. Accordingly, on August 3, 1955, a laparotomy was performed which revealed undue mobility of the stomach and transverse colon, as well as a marked redundancy of the transverse mesocolon. A new plication method for correction of the volvulus was effected: the transverse portions of the hepatic and splenic flexures were affixed to the ascending and descending colon, respectively. This was supplemented by fixation of the greater curvature to the transverse colon (figure 3). Following surgery it was evident that the stomach was pulled and held down to the transverse colon and was no longer able to undergo torsion. The patient made an uneventful convalescence and gave immediate proof of the effectiveness of the operation: postural changes failed to reproduce the abdominal discomfort evident preoperatively. Follow-up serial x-rays taken on August 30, 1955, likewise demonstrated the efficacy of the procedure; although freely movable to palpation, the stomach did not demonstrate the marked increase in mobility apparent on previous examination, while films obtained in all planes, including an upright steep Trendelenburg, anterior-posterior, posterior-anterior and both oblique positions, denoted ideal fixation of the stomach (figure 4).

Summary and Conclusions

1. A case of idiopathic gastric volvulus is added to the literature.

2. Acute gastric volvulus must be considered in the differential diagnosis of abdominal emergencies. In this regard one should keep in mind Borchardt's triad, viz., strong, vain efforts to vomit, circumscribed epigastric pain and resistance to passage of a stomach tube.

3. A new method of surgical correction is described; fixation of the stomach to the transverse colon and plication of the hepatic and splenic flexures serve to prevent volvulation of the stomach.

Summario in Interlingua

Cento casos de volvulo gastric se trova documentate in le litteratura depost que Berti primo describeva le condition in 1866. Le factores etiologic pote esser classificate sequentemente:

I. Intrinsec
  A. Congenite
    1. Anormalitates del mesenterio
    2. Eventration del diaphragma
    3. Stomacho bilocular
    4. Defectos del lobo sinistre del hepate
  B. Acquirite
    1. Hernia sinistro-diaphragmatic
    2. Tumores
    3. Displaciamento de organos vicin
    4. Processos inflammatori in le vicinitate del stomacho
II. Extrinsec
  A. Somatic
    1. Pression extra-abdominal
    2. Distension gastric
  B. Psychic

Proque le stomacho e le colon transverse es attachate al ligamento gastrocolic, le alteration del position de un de iste organos causa un rotation del altere.

Le triade de Borchardt es utile in diagnoses differential. Su tres factores es (1) dolor epigastric, (2) van tentativas de vomito, e (3) resistentia al passage del tubo gastric.

Quando medios medical non succede a reducer un volvulo, un urgente intervention chirurgic es possibilemente indicate pro prevenir strangulation.

Es presentate le reporto de un caso illustrative de recurrente volvulo gastric. Esseva usate in iste caso un nove methodo chirurgic sin resection gastric. Le methodo consisteva in fixar le plus grande curvatura del stomacho al colon transverse post que le colon transverse esseva immobilisate per le plication del flexuras hepatic e splenic. Un post-operative evalutation clinic e roentgenologic demonstrava le efficacia del methodo.

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TIETZE'S SYNDROME *

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TIETZE'S syndrome is a painful, nonsuppurative swelling of the costochondral or sternoclavicular junction. Since Tietze's original description in 1921,[1] over 100 patients with chest pain caused by this syndrome have been described by foreign authors. A search for reports concerning this entity in the American literature reveals that Tietze's syndrome has been discussed only twice: the first paper by Motulsky and Rohn in 1953,[2] and the second by Wehrmacher in 1955.[3]

In the differential diagnosis of chest pain, Tietze's syndrome should always be considered. Tenderness over the involved cartilage at times is extreme and may be exaggerated by effort as a result of increased thoracic movement. A small, firm, smooth mass may become palpable and visible in the involved costochondral junction.

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The scarcity of publications concerning this entity and the observation of two patients with Tietze's syndrome in the past year prompted this report.

Case Reports

Case 1. A 45 year old white man developed pain over the left side of his chest. Coughing and exertion increased the discomfort. He reported to his family physician, who suspected anginal attacks and requested cardiac consultation. Electrocardiographic studies, including the Master two-step exercise tests, were negative. Examination of the chest wall revealed a small, tender swelling of about 3 by 3 cm. at the third left costochondral junction. Procaine infiltration of the painful area gave immediate relief. A second examination six weeks later still revealed the small tender mass on palpation, but the discomfort was much less pronounced. Reassurance that the condition was benign and not cardiac in origin helped considerably in relieving the patient's anxiety state, so prominent on his first visit.

Case 2. A 50 year old white woman reported for examination complaining of severe pain in the upper left side of the chest. Moving about, doing her housework and lifting brought on the pain or made it worse. She was apprehensive and worried, and thought she had heart trouble. Electrocardiogram, Master two-step tests and chest x-ray were negative. Physical examination was normal except for the finding of a small tender swelling over the left second costochondral junction. Pressure over this area produced severe pain, which extended to the left shoulder and arm. Reassurance of the benign character of the disorder and local application of heat gave considerable relief. Three months later the small tender area was still present but the distress was much less pronounced. Procaine infiltration was refused.

Comment

The etiology of Tietze's syndrome is not known. Malnutrition, heavy lifting, repeated trauma from cough and sudden movements have been implicated as causal factors. The second costochondral junction is involved in about 60% of all cases. The presence of an interarticular sternocostal ligament in this area suggests that trauma or rheumatic disease of this ligament may be an important factor in the etiology of this syndrome.

No specific findings have been reported on x-ray examination, but radiologic examinations and other laboratory tests are helpful in excluding associated diseases producing chest pain. Tietze's syndrome is rather easily recognized if one just thinks of this possibility. In the differential diagnosis one must consider benign and malignant diseases within the chest wall, in the breasts, the lungs, heart and mediastinum.

In the treatment of this syndrome local applications of heat, procaine infiltrations, salicylates and reassurance of the benign character of the disease give relief in the majority of these cases.

Summary

Two cases of Tietze's syndrome are reported. In both patients angina pectoris was considered as a possible causative factor in the production of chest pain. Tietze's syndrome is a benign disease, characterized usually by a painful swelling of the costochondral junction. It is easily recognized if one just thinks of this possibility. Tietze's syndrome should be considered in the differential diagnosis of all conditions producing chest pain.

SUMMARIO IN INTERLINGUA

Le syndrome de Tietze es un dolorose nonsuppurative tumescentia del junction costochondral o sternoclavicular. Depost le description original presentate per Tietze in 1921, plus que 100 patientes con dolores thoracic causate per iste syndrome ha essite describite per autores al extero del Statos Unite. Le syndrome ha essite describite solmente duo vices in le litteratura american.

In le diagnose differential de dolores thoracic, le syndrome de Tietze deberea semper esser prendite in consideration. Le sensibilitate sub pression in le area supra le involvite cartilagine es frequentemente extreme e pote esser exaggerate per effortios resultante in augmentate movimentos del thorace. Un parve, firme, e lisie massa pote devenir palpabile e mesmo visibile in le involvite junction costochondral.

Le etiologia del syndrome non es cognoscite. Malnutrition, sublevar cargas pesante, e repetite occurrentias de trauma como resultato de tusse e subite movimentos ha essite mentionate como factores causal. Le secunde junction costochondral es involvite in circa 60% de omne casos. Le presentia de un ligamento sternocostal interarticular in iste area suggere que trauma o morbo rheumatic de ille ligamento es possibilemente un factor importante in le etiologia del syndrome de Tietze. Nulle constatationes specific ha essite reportate super le base de examines roentgenologic, sed tal examines e altere studios laboratorial pote esser utile per excluder morbos associate que produce dolores thoracic. Le syndrome de Tietze es facile a recognoscer si on pensa al possibilitate de su presentia. In le diagnose differential on debe prender in consideration benigne e maligne morbos intra le pariete thoracic, in le pectore, le pulmones, le corde, e le mediastino.

Il non existe un therapia specific, sed le application local de calor, salicylatos, infiltrationes de procaina, e—particularmente—le reassecuration que il se tracta de un morbo benigne resulta usualmente in le alleviamento del symptomas. In le presente articulo duo casos del syndrome de Tietze es reportate.

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ANAPHYLACTIC SHOCK FOLLOWING INTRAMUSCULAR THIAMINE CHLORIDE*

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IN view of the paucity of reported reactions to parenteral thiamine chloride in the literature, it was felt that this case might renew an active interest in this phenomenon. It is, furthermore, the only case of severe reaction following the

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intramuscular injection of thiamine chloride recorded at the Rhode Island Hospital over the last 10 years.

Case Report

This was the third Rhode Island Hospital admission of a 62 year old Italian truck driver, who was admitted on August 6, 1954, to the Neurological Service with the chief complaint of numbness and weakness of the left arm and hand of two hours' duration.

Past History: Thirty-eight years previously the patient had had Bell's palsy. He had been admitted to the Rhode Island Hospital for the first time 20 years prior to this admission because of back pain. Immobilization with a full body cast at that time afforded relief.

On September 1, 1949, he was admitted to the Rhode Island Hospital for the second time because of acute cardiorespiratory distress. Two to three months prior to this second admission the patient had complained of weakness and a 10 pound weight loss, and had been treated by his private physician with "liver injections" every day for the first week and every other day for the subsequent three weeks. Several hours before admission he had received 1 ml. of 20% thiamine intramuscularly from his physician. Twenty minutes later he had flushing of the face, dizziness, palpitation and sharp precordial pain. These symptoms lasted about 30 minutes, during which time his doctor gave him 1 ml. of Coramine, 0.5 mg. of digitoxin by mouth, and sublingual nitroglycerin, with subsidence of symptoms. He was brought to the hospital by ambulance.

Except for his having dyspnea after walking three flights of stairs, a "cigarette cough" productive of white sputum for years, the habit of drinking four to five glasses of beer daily, and having previously worked for many years in a flour mill, his past history on the second admission was essentially unrevealing. There were no known allergies.

He presented himself at that time as a well developed, obese male in no immediate distress. Temperature was 98.6° F.; pulse, 88 per minute; respirations, 20 per minute; blood pressure, 130/85 mm. Hg. The only positive physical findings were a slight deviation of the trachea to the right and inspiratory râles in the right upper anterior and left lower chest. His laboratory tests revealed a white blood count of 10,250 per mm^3, with a differential count of 67% polymorphonuclear leukocytes and 33% lymphocytes; a hemoglobin of 14.9 gm. per 100 ml.; an icterus index of 5.6 units; a thymol turbidity of 2 units; a blood urea nitrogen of 12 mg. per 100 ml.; a fasting blood sugar of 87 mg. per 100 ml.; a total protein of 7.7 gm. per 100 ml.; and an albumin of 4.2 gm. per 100 ml. His electrocardiogram was negative. The x-ray of his chest was interpreted as showing lungs that were normally aerated except for several tiny transverse lines of density in the left costophrenic sinus suggesting discoid atelectasis. The remainder of the x-ray film was negative. The patient was discharged on September 5, 1949, with the diagnosis of acute poisoning thought to be due to thiamine chloride.

In the interim between his second and third hospital admissions he had had three bouts of "pneumonia" with subsequent intermittent "bronchial trouble." His teeth had become more carious, and a cataract in his right eye had caused marked impairment of his vision. There was no history of additional toxic or allergic reactions. Only nocturia (twice nightly), occasional heartburn and constipation were volunteered as complaints.

Present Illness: Two hours prior to his third admission to the Rhode Island Hospital the patient noted the sudden onset of weakness of his left hand, followed by gradual numbness as well as tingling up to the midthird of his left upper arm. He also complained of a "heavy head" and generalized headache.

Physical examination showed him to be a well developed, well nourished male in no acute distress. Temperature was 99.2° F.; pulse, 70 per minute; respirations, 22 per minute; blood pressure, 128/90 mm. Hg. An immature lenticular opacity of the right eye caused marked depression of visual acuity, and there were A-V nicking and arteriolar narrowing in the left fundus. The uvula deviated slightly to the left, and when the patient blinked his left eye the left corner of his mouth retracted to the left. His chest was increased in anteroposterior diameter, the lungs were clear, and the heart was not remarkable except for distant heart sounds. On abdominal examination, only large inguinal rings were noted. His sense of touch was diminished over the left upper arm, and he was hyperesthetic over the left leg. There was weakness of his left hand grasp. Although the deep tendon reflexes were hyperactive on the left, no pathologic reflexes were elicited. The laboratory determinations consisted of a 12,700 white blood count per mm^3, with a differential count of 50% polymorphonuclear leukocytes, 47% lymphocytes, 2% monocytes and 1% eosinophils; a hemoglobin of 14.6 gm. per 100 ml.; an erythrocyte sedimentation rate (corrected) of 26 mm. per hour, and a hematocrit of 50%. The pressure and dynamics of the spinal fluid were normal. The spinal fluid contained a protein level of 41 mg. per 100 ml. and a normal cell count. An electrocardiogram and an electroencephalogram were interpreted as normal. The patient was considered to have had a minor cerebral vascular accident.

At 11:45 a.m. on August 13, 1954, five minutes after receiving 1 c.c. (100 mg.) of Betaxin (thiamine hydrochloride) intramuscularly (knowledge of previous reaction by this patient to this drug was unknown at this time), the patient became dyspneic and apprehensive, and developed generalized rubor and perspiration. His blood pressure at 12:00 noon was 50/? mm. Hg. At this time he complained of numbness and tingling of his feet. At 12:15 p.m. his blood pressure was not only unobtainable, but he was also in marked respiratory distress. Both wheezes and râles were heard over the lower chest. Levophed, 4 c.c. (equivalent to 4 mg. of Levophed base) in 1,000 c.c. of 5% dextrose and water, was begun immediately, as well as oxygen by nasal catheter at a rate of 6 L. per minute. Aminophylline (0.5 gm. with 1 c.c. of 2% procaine) was given intramuscularly. Approximately 20 minutes after the onset of the acute episode, when his blood pressure had risen to 90/60 mm. Hg, with a persistently rapid heart action, 0.4 mg. of atropine was given intravenously, followed by the slow intravenous injection of 2 ml. (20 mg.) of Benadryl. Shortly thereafter the patient's bronchospasm was markedly relieved, the râles in his chest began to clear, and his blood pressure was recorded at 110/84 mm. Hg. Pyribenzamine (50 mg.) was given by mouth, and as soon as the element of shock was controlled Levophed was discontinued. After having received ephedrine sulfate (25 mg.), together with Pyribenzamine (50 mg.) by mouth every six hours for six doses, the patient experienced an uneventful recovery.

An electrocardiogram taken during the acute episode disclosed a normal mechanism, with rare premature ventricular beats and a ventricular rate of 130 per minute. The T waves were of lower voltage and the P waves were larger than in the tracing recorded on August 7, 1954.

The patient was discharged in good health on August 25, 1954, with the following diagnoses: generalized arteriosclerosis, questionable thrombosis of the right middle cerebral artery due to unspecified cause, and anaphylactic shock secondary to thiamine chloride hypersensitivity.

Discussion

This patient clinically fulfills the necessary criteria for anaphylaxis and subsequent shock: (1) he had been given intramuscular thiamine chloride prior to

the last acute episode and presumably sensitized thereby; (2) there was a period of latency for antibody production; and (3) he was inadvertently reëxposed to the same potential allergen by the same parenteral route and then developed shock.

In retrospect, he had received small amounts of parenteral thiamine with each of his "liver injections." Clark,[2] in his analysis of the vitamin content of liver extracts (both the crude and the concentrated preparations) for parenteral use, omitted from his study the determination of the thiamine content of parenteral liver because he felt that this factor was negligible. Apparently, this was not so in our case. After receiving about 17 injections of liver parenterally over a one month period, our patient suffered an acute reaction when a concentrated solution of thiamine was given intramuscularly. In accord with the proponents of the toxic-reaction theory, he could be considered as having manifested cumulative toxic effects from thiamine on his second Rhode Island Hospital admission.

Jaros, Wnuck and de Beer [3] reviewed the literature and summarized the 203 reported cases of reactions to thiamine, in which there were two fatalities. Based on their experimental work, they concluded that thiamine overdosage caused a chemical toxicity due to excessive amounts of acetylcholine and possibly some histamine. Furthermore, they felt that patients with impaired excretion of thiamine and low physiologic tolerance to acetylcholine have cumulative effects from thiamine and consequently manifest toxic reactions. They summarized their findings by stating that it was "difficult to believe that thiamine could act as an allergen to produce allergic reactions."

Vitamin B_1 is an inextricable part of one's diet and must be consumed in optimal quantities daily [1] to ensure its maintenance at adequate levels in the tissues of the body both as the pyrophosphate and in the free state. But it is difficult to believe that five years following the first acute episode, and within five minutes of receiving 100 mg. of thiamine hydrochloride parenterally (no previous reactions to this used vial of Betaxin were noted), our case reëxperienced acute collapse simply on the basis of toxicity to vitamin B_1. The interval between reexposure and reaction to this vitamin was too short to be merely a toxic response. It is conceivable [4] that the pure, unaltered, synthetic chemical,[5] thiamine hydrochloride, may occasionally not only act as an allergen when given parenterally, but also cause anaphylaxis in a previously sensitized individual. Suggestive of this phenomenon is the series of events that culminated in our patient's second acute attack.

Epinephrine, on the other hand, was the mode of therapy recommended by Jaros et al.[3] in thiamine toxicity. It is of interest that l-norepinephrine supplemented by spasmolytic and antihistaminic agents was utilized effectively in our case.

Summary

A case is presented of anaphylactic shock due to intramuscular thiamine chloride occurring in the same individual on two separate occasions. Possible explanations for this reaction are cited.

Acknowledgment

It is a pleasure to express our appreciation to Dr. Marshall N. Fulton for his help in preparing this paper.

SUMMARIO IN INTERLINGUA

Le base del presente reporto es le evenimentos del secunde e del tertie admission de un 62-enne camionero italian al Hospital Rhode Island. Post le injection intramuscular de 1 ml de un concentration de 20 pro cento de thiamina ille esseva transportate per auto-ambulantia al hospital. Ille se trovava in un stato de acute angustia cardiorespiratori. Un medie hora ante su secunde admission, le 1 de septembre 1949, ille habeva recipite 1 ml de Coramina, 0,5 mg de digitoxina per via oral, e nitroglycerina sublingual, administrate per un medico qui habeva tractate le con "injectiones hepatic" durante un periodo de un mense. Gradualmente su vertigine, palpitationes, e un acute dolor precordial recedeva, e le rubor coperiente su obese corpore dispareva. Nulle cognoscite allergia esseva involvite. Intra cinque dies le patiente esseva dimittite in stato "meliorate" con le diagnose de acute invenenamento apparentemente debite a chlorido de thiamina.

Le patiente esseva re-admittite le 6 de augusto 1954 con signos e symptomas de un minor accidente cerebro-vascular. Un septimana plus tarde ille recipeva un injection intramuscular de hydrochlorido de thiamina (100 mg de Betaxina), e intra cinque minutas ille suffreva le symptomas de choc anaphylactic. Vinti minutas post que ille habeva recipite oxygeno per catheter nasal, Levophed in administration intravenose (4 mg de Levophed de base diluite in 1.000 ml de un concentration de 5 pro cento de dextrosa e aqua), e aminophyllina (con procaina in un concentration de 2 pro cento) per injection intramuscular, su pression sanguinee esseva registrate como 90/60 mm Hg. Brevemente plus tarde, atropina, Benadryl, sulfato de ephedrina, e etiam Pyribenzamina esseva empleate. Le patiente esseva dimittite in bon stato de sanitate le 25 de augusto 1954 con le sequente diagnoses: Arteriosclerosis generalisate, thrombosis dubitose del dextero-central arteria cerebral debite a un causa indeterminate, e choc anaphylactic secundari a hypersensibilitate a chlorido de thiamina.

Iste caso satisfaceva le criterios essential de anaphylaxis, i.e. sensibilisation a chlorido de thiamina, un periodo de stato latente, e duo immediate reactiones generalisate post separate re-expositiones al mesme antigeno potential. Pro iste ration le theoria del reaction toxic proponite in 1952 per Jaros, Wnuck, e de Beer non es acceptate pro iste caso. Nostre patiente esseva tractate efficacemente con l-norepinephrina supplementate per agentes spasmolytic e antihistaminic.

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ACUTE ACQUIRED HEMOLYTIC ANEMIA DUE TO DELAYED PRIMARY ATTACK OF VIVAX MALARIA *

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In many parts of the world malaria is still a common infection. Recognition of this fact is important to clinicians in the United States. Veterans of foreign service are still presenting the unusual manifestations of the delayed primary attack of vivax malaria, one of which is acute hemolytic anemia.[1, 2]

Primaquine has become an effective drug against the exo-erythrocytic stage of *Plasmodium vivax*.[3, 4] Primaquine and chloroquine are routinely administered to the troops returning from the endemic areas.[4, 5] A few cases of malaria still develop the delayed primary attacks and relapses. Some of these have unusually long incubation periods and their clinical symptoms are atypical.[6-9]

The purpose of this paper is to report an unusual case of acute acquired hemolytic anemia caused by a delayed primary attack of vivax malaria. Manifestations of this delayed primary attack created a baffling clinical picture. In spite of newer therapeutic methods, the delayed primary attacks still occur. Therefore, malaria continues to exist as a problem, especially in the Korean veterans and in people who have recently traveled in endemic areas.

Case Report

This 27 year old white male was admitted to the U. S. Army Hospital, Fort Carson, Colorado, on July 15, 1954. The patient stated he had returned from Korea in September, 1953. Aboard ship he took primaquine, 15 mg. each day for 14 days, and chloroquine, 0.3 gm. three times a day for one day, and then 0.3 gm. each day for two days. He felt well until July 1, 1954, at which time he developed anorexia. On July 13, 1954, he noted a temperature elevation to 100° F., associated with nausea and vomiting. On July 15, 1954, the day of admission, he noticed a dark discoloration in his urine. Intermittent chills and excessive perspiration were present. He stated that prior to admission he had taken aspirin and cold tablets of unknown type. In April, 1954, the patient was seen at the U. S. Army Hospital, Fort Carson, Colorado, for thrombophlebitis of his right leg. At that time he received anticoagulants, bedrest and an elastic bandage to the involved leg. After being discharged from the hospital, in May, 1954, the patient was asymptomatic until the onset of his present illness.

Physical examination revealed an obese 27 year old white male who appeared to be in moderate distress. The skin surfaces were pale. His temperature was 98.8° F. at the time of admission to the hospital. The spleen was somewhat tender and extended two fingerbreadths below the left costal margin. The liver edge was one fingerbreadth below the right costal margin. The remaining portion of the physical examination was within normal limits.

Laboratory studies revealed a red blood count of 2.6 million, a hemoglobin of 9 gm.%, a hematocrit of 27 mm. and a sedimentation rate of 65 mm. in 60 minutes.

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The differential peripheral blood count revealed 32% neutrophils, 60% lymphocytes, 3% eosinophils and 5% bands. There were moderate anisocytosis, slight poikilocytosis and polychromasia. The four initial thick and thin malaria smears taken during febrile periods were reported as negative. Agglutinations for typhoid, paratyphoid and brucella were normal. Stool specimens for blood, ova and parasites were negative. Stool cultures for enteric pathogens were normal. Urine test for urobilinogen revealed four Ehrlich's units per 135 c.c. of urine, and the fecal urobilinogen content was elevated to 450 mg. in a 24-hour specimen. Cardiolipin microflocculation test was negative. The Coombs' test was negative and the fragility test was normal. The initial reticulocyte count was 8%. A peripheral blood smear revealed 3% nucleated red cells. Two bone marrow aspirations were essentially normal. Serum bilirubin was 1.4 mg.% total, with .5 mg. indirect, .2 mg. direct. A Bromsulphalein test revealed 3.5% dye retention. Prothrombin time was 70% of normal. Cephalin flocculation test was 3 plus in 24 hours and 4 plus in 48 hours. The hemosiderin test performed on the urine specimen was reported as normal. The Hams acid test for paroxysmal nocturnal hemoglobinuria was reported as normal. The Rumpel-Leede armband constrictor test was normal. The Donath-Landsteiner test for paroxysmal cold hemoglobinuria was normal. The serum tested for free hemoglobin was normal. The plasma protein was normal and the heterophil test was normal. Smears for malaria parasites were taken daily until September 7, 1954.

After admission the patient's temperature rose to 100° F. each afternoon for a period of seven days. No chills were noted while the patient was observed in the hospital. Evidence of active hemolysis was manifested by an elevated reticulocyte count, nucleated red cells in the peripheral smear, elevated fecal urobilinogen and anemia. The patient was then placed on 80 units of ACTH in divided doses. The reticulocyte count gradually returned to normal, the hemoglobin rose to 15.5 gm. and the hematocrit to 48 mm. by September 3, 1954. On September 7, 1954, the first positive *Plasmodium vivax* malaria smear was obtained. After this the patient was placed on chloroquine, 0.3 gm. three times a day for one day and 0.3 gm. daily for two days, with primaquine, 15 mg. daily for 14 days. On completion of the therapy there was no evidence of hemolysis; the spleen had decreased in size and was no longer tender. The patient was essentially asymptomatic. Reëvaluation of the patient in November, 1954, revealed him to be asymptomatic, with a normal red count, reticulocyte count, hemoglobin and hematocrit.

Discussion

Occasionally the recognition of malaria in the delayed primary attack represents a difficult diagnostic problem.[8] In spite of chills and fever, the malaria smears may be negative. The onset of a delayed primary attack may be manifested by many unusual pictures, one of which is an acute acquired hemolytic anemia. When the malaria smears are initially negative, establishment of the diagnosis is difficult.

There is strong inferential evidence that the exo-erythrocytic infection of *Plasmodium vivax* persists in the liver of man. This may account for the late relapses.[3, 10-12] Primary delayed attacks have been reported 27 months after the initial infection.[6, 7, 9] Some patients are unduly sensitive in the primary delayed attacks to the malaria parasites.[10, 13] They may have a marked clinical reaction, and the anemia may depend on the rate of destruction plus the rate of regeneration of red blood cells.[13] Parasitized and nonparasitized cells may be destroyed in enormous numbers.[13] When malaria smears have been persistently negative, the subcutaneous injection of 0.5 to 1 ml. of 1–1000 epinephrine may be followed

by the appearance of plasmodia in the peripheral smear. The effectiveness of this test, however, has varied in different hands.[18] Repeated smears (on July 15, 1954, to September 7, 1954) were obtained in this case. In view of the long incubation period (10 months) and our inability to demonstrate malaria parasites in the peripheral smear, the etiology of the acute hemolytic process could not initially be established.

Conclusions

In spite of routine primaquine and chloroquine therapy administered to Korean veterans, cases of delayed primary attacks of malaria occasionally do occur after prolonged incubation periods. These problems present a more difficult diagnosis, inasmuch as there is usually a bizarre clinical picture, no history of previous malaria infection, and a greater incidence of negative initial smears. Delayed primary malaria must still be considered as a differential diagnosis when one is confronted with a problem of acute acquired hemolytic anemia, especially in Korean veterans.

Summario in Interlingua

In multe partes del mundo malaria es ancora un infection commun. Un del inusual manifestationes de tardive attaccos primari es acute anemia hemolytic. Certe tal casos ha longe periodos de incubation, e le symptomas clinic es frequentemente atypic. Le objectivo del presente reporto es demonstrar que malaria remane un problema in despecto del plus moderne methodos therapeutic. Le caso hic presentate illustra le facto que tardive attaccos primari debe esser prendite in consideration in le diagnose differential de acute anemia hemolytic, specialmente si le patiente in question es un veterano del campania in Corea o ha recentemente viagiate in altere areas endemic.

Un masculo blanc de 27 annos de etate retornava ab Corea in septembre 1953. Ille recipeva primaquina e chloroquina al bordo del nave durante su viage de retorno. Ille se trova ben usque le 1 de julio 1954. A iste tempore ille disveloppava anorexia e altiamento del temperatura. Le laboratorio revelava indicationes de hemolyse acute. Diurne frottis peripheric pro malaria esseva executate ab le 1 de julio 1954 usque al 7 de septembre 1954. A ille ultime data le prime positivitate pro *Plasmodium vivax* esseva trovate. Post tractamento con primaquina e chloroquina le symptomas dispareva completemente.

Il es evidente que le tardive attaccos primari de malaria post prolongate periodos de incubation presenta difficultates diagnostic. Le aspectos clinic es usualmente bizarre. Il ha nulle historia de un previe infection malarial e un alte incidentia de frottis initial negative. Tardive malaria primari deberea per consequente esser prendite in consideration como factor possibile in le diagnose differential in casos de patientes con acute acquirite anemia hemolytic si ille patientes ha recentemente sojornate in areas endemic.

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CHRONIC MENINGOCOCCEMIA *

By MAURICE GORE, M.D., *Chicago, Illinois*

CHRONIC meningococcemia without the presence of meningitis is an uncommon clinical entity, particularly when this occurs in an isolated instance. During local outbreaks or in endemic areas, meningococcemia occurs frequently and can be easily diagnosed. According to Feddersen,[1] the first description of chronic meningococcemia was published by Solomon.[2] Feddersen reported that there were over 100 cases in the European literature [3-6] up to 1945, and stated that there were fewer cases in the American literature [7-11] because full investigations were not the usual procedure. With the advent of sulfonamide therapy, treatment was often started before adequate diagnostic studies were made. Since meningococcemia responds so well to this therapy, it was reasonable to offer this fact to explain the infrequency of a definitive diagnosis.

During World War II a general increase in the occurrence of meningococcal infection was noted, particularly in relatively small areas where large numbers of people or troops were congregated. In such areas, where the frequency of the disease was increased, medical personnel were on the alert and the diagnosis was often made in the meningococcemic phase. At this stage prompt therapy aborted the disease, so that the cerebrospinal phase was never reached in its typical manifestations. In isolated cases the diagnosis of acute meningococcemia may be more difficult; and the diagnosis of chronic meningococcemia, with its protean manifestations, can be even more perplexing unless blood cultures are

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made. The diagnoses that are often made at the onset of this infection are influenza, migratory polyarthritis, rheumatic fever and erythema nodosum.

The picture usually encountered in chronic meningococcic septicemia is as follows: The patient is a young adult who has an acute onset of bouts of chills, fever, sweats, headaches, anorexia, malaise, and fleeting muscle and joint pains. The appearance of a rash, which is often petechial, is frequent and of diagnostic significance. The rash is often macular or papular or maculopapular, and often resembles erythema nodosum. There may be relative bradycardia, and leukocytosis is usually present. The periodicity of fever has been noted in many cases. The diagnosis is made by a positive blood culture and the identification of the microörganism. A positive blood culture is most often obtained when the blood is withdrawn at the height of fever.

The following case is reported because it very clearly illustrates the typical clinical features of chronic meningococcemia. There are, in addition, other facts in the history that provoke considerable clinical and immunologic speculation.

Case Report

A well developed, well nourished 36 year old white male was admitted to the Veterans' Hospital, Hines, Illinois, on March 20, 1947. He was very tense, apprehensive and fearful of dying, and complained bitterly of chills, fever, joint pains (especially in the wrists), red nodules on the skin which would come and go, and, most recently, a marked nervousness.

The patient maintained that he had been in good health until November, 1946, at which time he developed chills and fever. There were some swelling and pain in the right knee, followed by swelling and pain in both ankle joints which prevented him from walking. After a few days these symptoms subsided and then recurred shortly thereafter. Since then he had had pain in the joints of both knees, ankles, elbows and wrists. In addition to the joint pains, there were swelling, local redness and heat. The past history was very significant in that, while on active duty, he had had cerebrospinal meningitis on two occasions. Army records confirmed that the first attack was in February, 1944, and the second in September, 1945. The disease was stated to be the "epidemic" type. On both occasions the patient was treated with sulfadiazine, with very favorable results. At one time he was also treated for malaria. The remainder of the history was essentially negative and did not contribute any pertinent data.

On admission to the hospital the patient's temperature was 101° F., orally; pulse, 120; respirations, 20 per minute. The examination of the head and neck was negative, and there was no evidence of any meningeal irritation. Examination of the chest revealed no evidence of any pulmonary or cardiovascular abnormalities. Abdominal examination was negative, noting particularly the absence of any hepatomegaly or splenomegaly. The right wrist was red, slightly swollen, warm and tender upon pressure over the radial aspect. There were numerous red nodules, 1 cm. in diameter, over the extensor surfaces of the forearms and over the anterior aspect of the legs. These nodules were tender and blanched under pressure. The initial impression was that the patient had a migratory polyarthritis of rheumatic origin which was associated with rheumatic subcutaneous nodules.

The laboratory data on admission revealed normal urine and negative serologic test for syphilis. There was no anemia, but the leukocyte count was 24,000, with 87% polymorphonuclears. The sedimentation rate (Wintrobe) was 28 mm. in one hour. The electrocardiogram was within normal limits, and roentgen studies of

the various joints gave no abnormal findings. Polyagglutinations, urine cultures, sputum examinations and initial blood cultures were all negative.

After 15 days of symptomatic therapy with salicylates and codeine, a blood culture revealed gram-negative diplococci which proved to be meningococci. The salicylate and codeine therapy, which had failed to alter the clinical picture significantly, was discontinued. The patient was then given an initial oral dose of 4.0 gm. of sulfadiazine, followed by 1.0 gm. every four hours, and 60,000 units of penicillin intramuscularly every three hours. At the end of 24 hours after institution of this therapy the patient was afebrile and nearly asymptomatic. Thirty-six hours after the beginning of treatment the skin lesions had cleared and the patient's mental attitude had changed completely, to one of optimism and cheerfulness. After two weeks of therapy blood cultures were sterile; the leukocyte count was 7,300, with 60% polymorphonuclears, and the sedimentation rate was 3.0 mm. in one hour. The patient was granted a two week leave of absence, and upon his return to the hospital his blood cultures were negative, and subsequent blood counts and sedimentation rates were normal. Shortly thereafter he was given his discharge from the hospital.

On January 13, 1948, and on February 19, 1954 (nine months, and six years and nine months, respectively, after his discharge from the hospital), communications were received from the patient stating that he was in good health and had not experienced any recurrences of the original symptoms. He considered himself in good health and had required no medical care since his discharge.

This patient was seen in December, 1954, and at that time had no complaints, particularly in reference to the illness described above. The physical examination was completely negative. Because of reports in the recent literature [12-16] relative to agammaglobulinemia in individuals manifesting poor antibody formation, a gamma globulin determination was performed at the Chicago Wesley Memorial Hospital and found to be normal.

Discussion

This case report serves to bring to our attention the fact that meningococcus can be the etiologic factor in chronic febrile conditions. Blood cultures are of course indispensable in making the diagnosis.

In addition to the eliciting of the facts of this case, with its very interesting story, the history the patient gave relative to the two preceding attacks of meningococcic meningitis prior to his development of the chronic septicemia provokes speculation.

Because of prompt treatment the patient may have failed to develop immunity against the type or types of meningococcus with which he was infected in 1944 and 1945. The present illness may have been another reinfection. On the other hand the patient may have been a carrier of these microörganisms, without an acute exacerbation until the episode during which he came under our care.

Summary

A case of chronic meningococcemic septicemia is presented which is very consistent with the typical picture encountered. The very interesting feature in the history of this case is the occurrence of two previous attacks of acute meningococcic cerebrospinal meningitis.

SUMMARIO IN INTERLINGUA

Chronic meningococcemia esseva primo describite in 1902. Usque 1945, circa 100 casos habeva essite reportate in le litteratura europee. Un minus grande numero de casos esseva reportate in le litteratura american. Le precoce uso de sulfonamidos e de antibioticos in le tractamento de morbos febril es possibilemente un factor definite a explicar le non-establimento del diagnose in le absentia de specific procedimentos laboratorial.

Le manifestationes proteiforme de iste morbo, su signos e symptomas, e le methodos del diagnose es discutite. Le morbo es frequentemente confundite con influenza, polyarthritis migratori, febre rheumatic, e erythema nodose. Un cultura sanguinee de positivitate pro meningococcos servi a establir le diagnose.

Es presentate un caso in que le plus inusual aspecto esseva un historia de duo previe attaccos de meningococcic meningitis cerebrospinal. Iste attaccos antecedente habeva essite tractate con successo per sulfadiazina. Le patiente esseva primo vidite post quatro menses de un morbo febril, characterisate per un polyarthritis migratori, nodulos rubie al extremitates que resimilava erythema nodose e leucocytosis. Indicationes de involvimento meningeal esseva absente. Un cultura sanguinee revelava meningococcos. Un curso de sulfadiazina e penicillina resultava in un recovramento routinari. Studios de consecution a periodos de usque a sex annos post le attacco indicava un continuate stato de bon sanitate e nulle recurrentia del symptomas.

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TRICHOSTRONGYLUS INFESTATION WITH PROFOUND EOSINOPHILIA*

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INTRODUCTION

Although trichostrongyliasis of humans is commonly found in such areas as Turkey, Iran, India, Japan, Korea and China, very few cases have been reported in the United States.[1-5] Although there are various species of this parasite which infest animals *Trichostrongylus orientalis* is the species found in man in areas of heavy human infestation.

The condition is so rare in this country that such common standard texts on gastroenterology as Bockus and Portis contain no mention of it.

FIG. 1. Egg of trichostrongylus sp. showing larval development. Approx. 500 × —actual size 91.5 μ × 46 μ.

Trichostrongyliasis is a nematode infection which is probably acquired by ingestion of the filariform larvae. The adult form inhabits the upper small intestine. The laboratory diagnosis is dependent upon the recovery of the ova from the feces. It is commonly a parasite of goats and sheep, and is believed to be transmitted by the handling of contaminated soil or food. An untrained observer will easily confuse the ovum with that of hookworm.

Our case reports are of interest primarily because of the diagnostic problem which presented itself, the unusually high eosinophilia, the presence of this condition in husband and wife, and its rare occurrence in the United States.

The return of our servicemen from endemic areas renders this entity of more than academic interest.

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Case Reports

Case 1. This 43 year old white male corpsman was hospitalized on April 20, 1954, for complaints of abdominal pain, diarrhea and weakness. Two weeks prior to entry he had noted a dull, sickening sensation diffusely across his upper abdomen and lower anterior chest. This was not sharp. There was no nausea, vomiting or cramping. He felt best while lying down quietly without moving about. The sensation lasted for hours and appeared to be increased immediately after eating.

Diarrhea had been noted for 10 days prior to entry. It was watery, contained no blood, and averaged 10 to 16 movements daily.

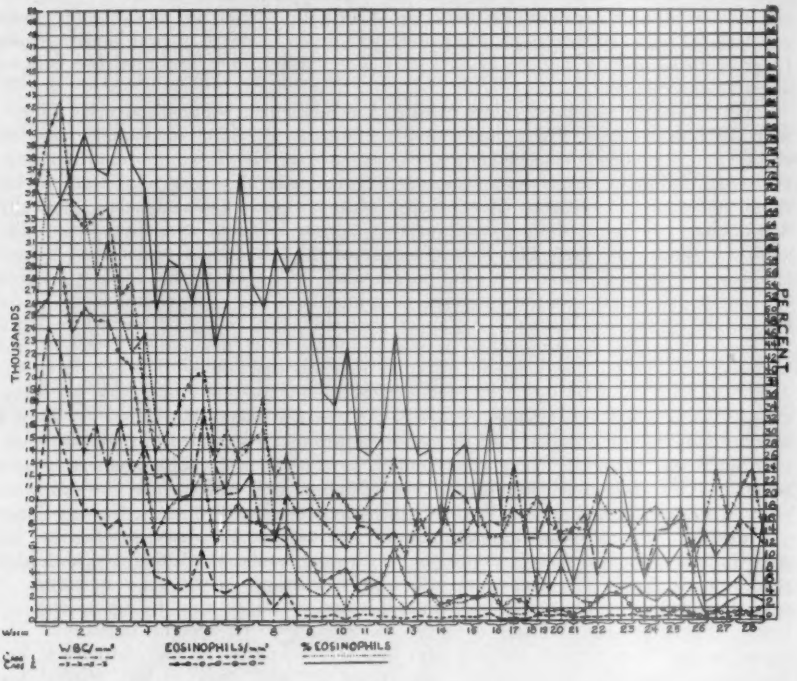

Fig. 2.

Increasing weakness, fatigue and dizziness had been apparent for four days prior to entry. The patient believed he had had a weight loss of about 12 pounds in the previous two weeks.

There were no complaints referable to the genitourinary, cardiovascular or respiratory systems.

Past history revealed that the patient had been born in southern Italy, where he had lived until the age of nine. In 1942 he spent one month in Panama, and in 1949 was in Korea for one year.

Except for the usual childhood illnesses his only medical history of note was infectious mononucleosis in 1948, at which time he was ill for six weeks. Multiple infiltrations in the lung were discovered upon his return from Korea; serial chest

x-rays since have revealed no change, and the presumptive diagnosis has been histoplasmosis or tuberculomas.

This soldier and his wife had a garden for which they used sheep manure as a fertilizer.

Physical examination revealed a chronically ill, dehydrated patient with no remarkable physical findings except for slight tenderness along the right costal margin. No punch tenderness over the liver was elicited. Blood pressure, 92/60 mm. of Hg; pulse, 80.

Hospital Course: After two weeks the patient gradually began to show improvement, and within one month was fairly well except for infrequent bouts of diarrhea and upper abdominal pain. The treatment was symptomatic, primarily paregoric and milk of bismuth for diarrhea, and codeine for pain. After the causative organism was isolated on a few occasions, the patient was given a course of oral gentian violet (1 grain three times a day for 21 days) six weeks after entry, and then two courses of tetrachloroethylene.

On admission the blood count revealed the following: white blood cells, 17,900, with 37% neutrophils, 9% lymphocytes, 1% monocytes, 52% eosinophils and 1% basophils. Subsequent blood counts are noted in chart 1. Prior to definitive diagnosis, the following tests were performed: Trichinella skin test was negative for three consecutive weeks. A liver biopsy was normal. Bromsulphalein, cephalin flocculation, prothrombin time, total protein, serum bilirubin and thymol turbidity were all normal on April 29. Muscle biopsy of the left deltoid region was normal on May 14. A bone marrow aspiration revealed 42% eosinophilia on May 11, but the pathologist noted that the specimen contained "too much peripheral blood." An electrocardiogram was normal. An upper gastrointestinal x-ray performed on April 28 revealed marked hypermobility of the small bowel at five hours. Barium was scattered through the distal half of the small intestine and colon. The pattern of the distal one-half was nonspecifically abnormal and could be due either to small bowel allergy or to distal small bowel parasites. A barium enema performed on May 4 was normal. Chest x-ray showed the abnormalities remarked upon in the past illness, with no recent changes. Daily stool studies were performed. The stools were first found to have trichostrongylus on May 14 (24 days after entry), and the ova were seen on subsequent occasions. These findings were verified by Dr. E. Carroll Faust.

Case 2. This 43 year old white female, wife of case 1, entered the hospital six days following her husband's admission, with complaints of abdominal pain, back pain and diarrhea. The abdominal pain had begun three weeks prior to entry. It was sharp but not cramping in nature, and lasted for a few minutes up to one-half hour. It was present diffusely over the abdomen, with no specific radiation. The backache had been present for five days and was primarily in the midthoracic and lumbosacral regions. Diarrhea had been noted for four days; it was watery, and there were as many as 12 movements daily, free of blood or pus. There were no complaints referable to the genitourinary, cardiovascular or respiratory systems. The patient had gone through the menopause four years previously.

Past history was noncontributory. The patient had never been outside the United States.

Physical examination revealed a somewhat obese female in no distress and with no significantly abnormal physical findings.

Course in Hospital: In the hospital the patient had an intermittent diarrhea which gradually subsided over a period of six weeks. The only other complaints noted were occasional episodes of diffuse abdominal pain and backache. During the last month of hospitalization the patient felt well and was asymptomatic. Trichinella skin tests performed during the first and second weeks of hospitalization were negative on each occasion. The admission blood count revealed the following: 35,750 white blood cells, with 16% polymorphonuclear leukocytes, 13% lymphocytes and 71% eosinophils.

The first occasion the trichostrongylus ova were noted in the stool was six weeks after entry, or nine weeks after the onset of symptoms. Stool specimens were studied daily from the date of entry into the hospital. After seven months of observation only very occasional ova were observed (about one per week). No specific therapy was given.

Discussion

The profound eosinophilia present in both these cases and noted on chart 1 has not generally been reported in association with this infection. In fact, the severe eosinophilia led us originally to consider parasitic diseases such as trichinosis, the most likely cause, when we were able to rule out the other more common causes of marked eosinophilia.

The fact that the wife had never been outside of the United States is of interest, since the source of the infection was either the husband, or a common source from which both husband and wife were infected (possibly sheep manure).

The case of the husband may represent an initial infection in this country, as the patient had had no gastrointestinal symptoms since his return from Korea in 1950, thus having been in the United States for a period of four years prior to the onset of the present symptomatology. Daily stool specimens failed to reveal the organism for 24 days, a fact which would tend to implicate a recent rather than an old infestation. It must be stated, however, that asymptomatology is common in this infestation.

It is to be noted that about six weeks elapsed in the case of the soldier, and nine weeks in his wife's instance, from the time of onset of symptomatology to the time of recovery of the trichostrongylus in the stool.

Although the disease is quite rare in the United States, numerous articles have pointed out its frequency of occurrence in individuals coming from areas in which the disease is endemic, and it must be borne in mind as a possible etiology of eosinophilia.

It is of interest that this couple gave a history of gardening and of having used sheep manure for about one month prior to onset of their symptoms.

An attempt was made to get species identification by culture of the ova in a sheep; however, this was not successfully accomplished, despite the implantation of numerous ova in a susceptible sheep. When the technic was reviewed, it was felt that the ova were not sufficiently free of the isolating media and perhaps were nonviable. The ova were incubated in vitro and numerous larvae were obtained.

The marked eosinophilia has not been noted in the cases previously reported in this country. An eosinophilia of about 15% has been recorded.[5] The soldier ran an eosinophilia of up to 74% at the time the total white blood count was 24,000; his wife ran as high as 81% eosinophils at the time that a total white count was 26,800. The accompanying chart indicates the duration of both the eosinophilia and the leukocytosis.

In common with other reports, no specific therapy has been found. The infestations in our cases apparently burned themselves out as to intensity, but occasional ova were still noted after the patients were asymptomatic. The usual treatment with agents known to help eradicate hookworm has been repeatedly shown to be of no value.

The laboratory differentiation on appearance of the ova of trichostrongylus from the ova of ancylostoma (hookworm) is quite difficult unless the average ovum diameter is kept in mind. It will be noted that the ovum size is uniformly

average in trichostrongylus. The diameter of this ovum is 20 to 30 micra greater than that of the ancylostoma. The standard textbooks on parasitology discuss the differentiation in detail.

Summary

1. Two cases of trichostrongylus infestation with profound eosinophilia and marked leukocytosis are reported.
2. One patient definitely contracted the disease in the United States, the second may have done so.
3. The accurate differentiation of trichostrongylus ova from hookworm must be borne in mind if other cases are not to be overlooked.

Summario in Interlingua

Ben que trichostrongylosis es communmente trovate in Asia, le casos reportate in le Statos Unite es multo rar.

Trichostrongylosis es un infection nematodic que se acquire probabilemente per le ingestion de larvas filariforme. Le forma adulte de Trichostrongylus habita le intestino tenue. Le diagnose laboratorial de trichostrongylosis depende del identification del ovos de Trichostrongylus in le feces. Trichostrongylus es communmente un parasito de capros e oves. On crede que illo es transmittite per le manipulation de terra o de alimentos contaminate. Le observator inexperte pote facilemente confunder le ovos de Trichostrongylus con le ovos de Ankylostoma. Tamen, le diametro medie del ovos de Trichostrongylus es plus grande (20 a 30 μ).

Es reportate duo casos de iste infection, in un soldato e su uxor. Le cursos clinic esseva multo simile, characterisate per diarrhea e dolores abdominal. Le aspectos le plus inusual esseva un eosinophilia de inter 70 e 80% e un leucocytosis que variava frequentemente inter 20 e 30 milles. Le infection clinic del soldato comenciava tres septimanas ante illo de su uxor. Ille habeva essite in Corea quatro annos previemente, sed ille habeva habite nulle symptomatologia. Su uxor habeva nunquam essite foras del Statos Unite. Le duo habeva un jardin in que illes usava stercore de ove, sed difficultates technic preveniva le demonstration que isto esseva le fonte del infection. Esseva notate que in despecto del facto que feces diurne esseva studiate, plure septimanas passava ab le tempore del declaration del diarrhea usque al tempore del identification del organismo in le feces. Nos opina que o le infection in ambe patientes habeva un origine commun in iste pais o le uxor esseva inficite per su marito in caso que ille attrappava le condition in Corea.

Le infection recedeva gradualmente. Post un intervallo de plure menses le ovos esseva incontrate infrequentissimemente. Nulle therapie specific se provava de valor.

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EDITORIAL

EPIDEMIOLOGY OF SARCOIDOSIS

THE application of epidemiologic methods to the study of sarcoidosis has yielded information which though difficult to interpret has, nevertheless, indicated fruitful avenues for further study of various aspects of the etiology and pathogenesis of this obscure disease. Perhaps the term syndrome rather than disease should be used, for it is probable that several etiologic agents can produce the disease picture of what is now known as "sarcoidosis." As examples, some forms of histoplasmosis, berylliosis and cryptococcosis can be responsible for a clinical and histologic picture indistinguishable in practically all respects from that of sarcoidosis. Only refined pathological, mycological, chemical and epidemiologic studies can differentiate these entities. Furthermore, the sarcoid tubercle, the histologic hallmark of the disease, can be evoked by a variety of microbial agents, by particulate matter and by carcinoma in regional lymph nodes, to name a few. It is safe to assume that other etiologic agents capable of inciting the syndrome will be uncovered with further study. This discussion concerns, so far as possible, the disease "of unknown etiology"—those instances in which presumably histoplasmosis, beryllium disease, etc., have been eliminated.

The voluminous literature on sarcoidosis is devoted in the main to clarifying its clinical features, its pathology and to elucidating its relationship, if any, to tuberculosis. Scattered mention of possible epidemiologic significance has appeared. For example, in Schaumann's classic report wherein he demonstrated the systemic nature of the previously described cutaneous "Boeck's sarcoid" (more properly "Hutchinson's sarcoid") and lupus pernio of Besnier, five patients were described.[1] Included in this group was a "paysanne," an "agriculteur," and a "femme d'agriculteur," all undoubtedly of rural origin. Longcope and Pierson drew attention to the frequency with which sarcoidosis was found among members of farming communities.[2] Refvem, in Sweden, noted that sarcoidosis was a disease of "people living in the country, especially farmers, gardeners, etc." [3] That the disease was more apt to be noted in Negroes and among those from the Southern United States was also commented upon by Longcope, and others.[4]

The familial occurrence of sarcoidosis has been mentioned in several

[1] Schaumann, J.: Étude sur le lupus pernio et ses rapport avec les sarcoides cutanées, Ann. de dermat. et syph. **1**: 5, 1917.

[2] Longcope, W. T., and Pierson, J. W.: Boeck's sarcoid (sarcoidosis), Bull. Johns Hopkins Hosp. **60**: 223, 1937.

[3] Refvem, O. I.: Chronic granulomas in the alimentary tract caused by minute mineral particles. II. "Boeck's disease" and occurrence of minute mineral particles (preliminary report), Acta Path. **25**: 107, 1948.

[4] Longcope, W. T.: Sarcoidosis or Besnier-Boeck-Schaumann disease, J. A. M. A. **117**: 1321, 1941.

studies, and its presence in identical twins recorded.[5] Yet, its true incidence in any given locale, or indeed, in any country is difficult to determine. There are undoubtedly many cases that escape detection because of the asymptomatic pulmonary infiltrates or insignificant skin lesions. The study of servicemen, to be discussed below, gives as true a picture of incidence for a selected age and sex group as is available. Since all servicemen had at least two chest films, one on induction and one upon discharge from the service, much unsuspected disease would be uncovered. In the military personnel during World War II, 297 cases were found for an attack rate of 2.1 per 100,000 inductees. In Swiss army recruits there was an incidence of 13 per 100,000.[6]

Studies of the 297 cases of histologically proved sarcoidosis occurring among military personnel during World War II have strengthened and amplified earlier clinical impressions of certain epidemiologic features and have shed new light on this aspect of the disease.[7, 8] For servicemen from the South Atlantic Gulf Coast States (Region I) the attack rate was 6.3 per 100,000; for those from the Middle Atlantic and Border States (Region II) 1.5 per 100,000; and for those from the rest of the United States (Region III) 0.7 per 100,000. Thus, a definite concentration of cases by birthplace was noted for servicemen from the Southeastern and Gulf Coast States. Contrariwise, an analysis of the records of 117 patients with sarcoidosis seen at the Mayo Clinic from 1940 through 1951 did not confirm this geographic localization.[9] The rates, however, were calculated as percentage of cases of sarcoidosis compared to the total percentage of all admissions to the Clinic from various sections of the country. This does not provide precise information as to the relative incidence of the disease in an unselected population as does the Army series. Israel and Sones,[10] however, noted that 64 of the 74 Negroes they studied in Philadelphia were from the Southeast. This was a higher percentage than the estimated percentage of Southern-born Negroes in Philadelphia.

In the Army series it was noted that the majority of cases were from servicemen born in rural areas. When rates were calculated by population density of counties of residence or by actual location of place of residence, the predominantly rural distribution was confirmed. An 18/1, 22/1 and 17/1 ratio of cases in Negro servicemen to white servicemen was noted in

[5] Bickerstaff, E. R.: The familial aspects of sarcoidosis, Brit. J. Tuberc. and Dis. Chest **43**: 112, 1949.

[6] Schonholzer, G.: Morbus Besnier-Boeck-Schaumann; und Armeedurch-Leuchtung, Schweiz. med. Wchnschr. **77**: 585, 1947.

[7] Michael, M., Jr., Cole, R. M. Beeson, P. B., and Olson, B. J.: Sarcoidosis. Preliminary report on a study of 350 cases with special reference to epidemiology, Am. Rev. Tuberc. **62**: 403, 1950.

[8] Gentry, J. T. Nitowsky, H. M., and Michael, M., Jr.: Studies on the epidemiology of sarcoidosis in the United States: the relationship to soil areas and to urban rural residence, J. Clin. Investigation **34**: 1839, 1955.

[9] Carr, D. T., and Gage, R. P.: The geographic distribution of sarcoidosis, Am. Rev. Tuberc. **70**: 899, 1954.

[10] Israel, H. T., and Sones, M.: Sarcoidosis, Am. Pract. and Digest Treat. **3**: 18, 1952.

Regions I, II and III, respectively. That the concentration of cases in the South was not due exclusively to the large Negro population in those regions was apparent. There was a striking concentration of cases below the fall line, the geologic landmark indicating the former coast line of the United States. Those cases below the fall line appeared to be concentrated in areas where the surface materials are comprised of a fairly uniform type, of a sandy light colored soil. These soils are generally well-drained, low in organic and mineral plant nutrients and find their source from parent rocks which represent the major concentration of beryllium containing surface ore in the United States. This, of course, proved an attractive lead in view of the similarities between sarcoidosis and the disease produced by inhalation of beryllium fumes. Thus far, no excessive amounts of beryllium have been found in soils taken from random areas of residence of patients with sarcoidosis nor has beryllium been isolated from the tissues of patients with sarcoidosis. These features do not, however, vitiate "naturally occurring berylliosis" as being synonymous with sarcoidosis. However, until a closer association of clinical cases of sarcoidosis with naturally occurring beryllium is demonstrated and until beryllium compounds in native soils (or water) are shown capable of producing the features of sarcoidosis this intriguing etiologic lead cannot be accepted with finality.

Cummings [11] and co-workers have analyzed the 1194 cases of sarcoidosis diagnosed in Veteran Administration hospitals between 1949 and 1954. The distribution of birthplaces of the Negro veterans confirms the earlier studies of the military group, none of whom was included in Cummings' survey. However, contrary to the study of military personnel there was a significant number of cases in veterans who were born in the New England and North Central States. The hospitalization rate was 3.3 per 100,000 for white World War II veterans and 40.1 per 100,000 for Negro World War II veterans, a ratio of 12/1, which is a somewhat lower figure than recorded for the Army group. The rural location of birthplace still was noted, particularly in those from the Southeast.

On the basis of the review of the veterans cases, it is tempting to question whether the newer defined "endemic areas" of the New England and the North Central states represent hitherto unsuspected foci of sarcoidosis or whether they represent those veterans who contracted sarcoidosis while serving in military camps located in the Southeast. Since the incubation period of sarcoidosis is unknown, the time to anticipate such cases is unknown. Patients have been observed in whom sarcoidosis became manifest from 2 to 40 years after leaving the "so-called" endemic area. Even if one were to assume further contact with the agent (or agents) one would find it exceedingly difficult, if not impossible, to pinpoint the actual onset of a disease with such clinical vagaries and insidiousness as sarcoidosis. It is

[11] Cummings, M. M., Dunner, E., Schmidt, R. H., Jr., and Barnwell, J. B.: Concepts of epidemiology of sarcoidosis, Postgrad. Med. **19**: 437, 1956.

probably safe to assume, however, that the incubation period is in terms of years, not unlike that of leprosy. Since the new foci in the veterans' group are rather circumscribed, it is not likely that these cases represent those contracted in the Southeast while on military duty, but are rather those acquired in their native climes. Cummings et al. noted that these new areas do not correspond with the soil distribution of birthplaces noted in the Army series, but that they do correspond with the pine forest distribution in the United States. This hypothesis was advanced earlier in preliminary studies of the Army group and though not abandoned was "shelved" for lack of closer correlations. These newer studies should awaken interest in this hypothesis. It would not be necessary to postulate inhalation of only pine products for the production of sarcoidosis. It is not too far afield to hypothecate an unknown bacteria, virus, fungus or, indeed, protozoa that finds a fertile field for propagation in the pine forests.

From these extensive, yet incomplete epidemiologic data, that have accumulated over the years, certain facts have emerged. If one is to judge from the volume of medical literature, the chief foci of sarcoidosis appear to be in the United States, the British Isles, the Scandinavian countries, France, Germany and Switzerland, though no region of the world seems to have been free of the disease. That the disease has a predilection for those from rural areas is apparent from the reports from abroad and from the more statistically valid studies of the Armed Forces and Veterans groups in this country. Furthermore, the predilection of the disease for Negroes as suggested by earlier writers has been confirmed and amplified by the two latter studies. In other countries where the disease has been studied the Negro population is insignificant. No valid figures are available from the African continent. Furthermore, studies in this country indicate endemic foci chiefly in the Southeast and, perhaps to a less extent in New England and in the Midwest. The causes of such concentration are not apparent at this time. The suggestion of association with soils or with pine forests is attractive but not conclusive.

It is profitable to speculate as to the possible significance of these findings and to point up further avenues of approach. The predominance of cases among rural inhabitants of the Southeast, and particularly among Negroes naturally suggests several possibilities.

(1) The etiologic agent (or agents) either exists in higher concentration in this area or finds conditions of climate or rainfall or for symbiosis with other agents more favorable for its propagation. Concentration of an etiologic agent in a localized region calls to mind such fungal diseases as histoplasmosis and coccidioidomycosis.

(2) Vectors may exist in the "endemic foci" which facilitate transmission of the agent to susceptible hosts.

(3) The living habits in rural areas with the resulting more intimate contact with flora, fauna, and soils would permit prolonged exposure to an

agent, which though widely distributed in the non-arid sections of this country does not have such ready access to the host.

(4) Individuals living in these areas are so constituted or have their reaction capacity so altered by environment, diet, or habits, that they respond with the sarcoid reaction to an agent (or agents) which in other sections of the country produces different disease pictures. This seems the least attractive conclusion to draw. Nevertheless, it does appear that the Negro is much more susceptible to the disease than is the white, particularly when he resides in the rural Southeast. As indicated previously, there are no data as to the incidence of sarcoidosis in regions of Africa from whence the American Negro stems.

(5) The epidemiologic patterns noted in this country substantially vitiate the hypotheses that sarcoidosis is a form of tuberculosis, for it is surely completely inconsistent with the geographic distribution of tuberculosis in this country. That occasional cases might represent an exceedingly rare reaction to the human tubercle bacillus cannot be denied; one has only to consider the occasional case of histoplasmosis which can also cause such a picture. But in that case one is not dealing with the topic under discussion —sarcoidosis, a disease of unknown etiology.

Thus, it would seem that promising leads as to the etiology and pathogeneses of sarcoidosis have been furnished by the epidemiologic findings. Fruitful fields for further pursuit appear to be in the following areas:

(1) Careful assessment of the living habits, occupation, and environment of cases of sarcoidosis occurring outside the so-called "endemic areas"; (2) further field mycologic studies in the endemic areas; (3) reëxamination of the veteran population with the next decade in an attempt to establish whether sarcoidosis was contracted while on military duty in the Southeast. If such appears to be the case then much can be learned as to incubation period and intimacy of contact with the environment needed for production of the disease; (4) a broadened attack on the potentialities of naturally occurring beryllium for evoking the sarcoid reaction; (5) further attempts to split off from the syndrome of sarcoidosis those cases caused by now known specific agents capable of producing the picture.

MAX MICHAEL, JR., M.D.

REVIEWS

The Body Fluids: Basic Physiology and Practical Therapeutics. By J. Russell Elkinton, M.D., and T. S. Danowski, M.D. 626 pages; 15.5 × 23.5 cm. The Williams and Wilkins Co., Baltimore. 1955. Price, $10.00.

Of the many books which have appeared in the past few years on the subject of fluid and electrolyte metabolism, this is by far the most comprehensive and intelligibly written. Although the authors have publicly stated some very strong views on various aspects of this subject, they have succeeded in producing a considered exposition which encompasses many different concepts and permits the reader to come to his own conclusions.

The initial chapter on Body Fluid Dynamics is a valuable contribution and it should aid the uninitiated in developing a comprehensive philosophy of fluid metabolism.

The chapter on Paleochemistry is a condensation of work which has been more effectively covered in other sources, particularly in the various books of Homer Smith and does not contribute significantly to the overall picture.

The information on Methods of Studying Body Fluid Distribution is to be found only in highly specialized works and will be of great help to students and clinicians who are interested in the means by which the data in current literature are accumulated.

The second part of the volume is concerned with basic principles as related to clinical situations and a number of well chosen case studies are presented.

The third part deals with specific disease entities and, as is to be expected from the bent of the authors, the major emphasis is on renal failure. The fluid and electrolyte imbalance of congestive heart failure is presented as an alteration in the steady state, a stimulating approach.

Eleven pages are devoted to diabetic ketosis, and here some relatively naive concepts are introduced, reflecting the authors' lack of interest in intermediary metabolism as opposed to electrolyte physiology.

There is an excellent chapter on vivodialysis which should be of value increasingly in the future as more use is made of the artificial kidney.

There are a number of small errors, probably of proof reading, and several of the diagrams have extra chemical bonds or incorrect labels. Some statements are made which are rather confusing; for example, the definition of titratable acid on page 253 seems to imply that there are different concentrations of phosphate at one pH and at another in the urine. The statement on page 117 that the volume of distribution of sucrose represents both the middle and the lower values for the extracellular space makes no sense. A number of outmoded concepts such as "fixed base" are perpetuated and little attempt is made to introduce the more modern concepts of acid base equilibrium.

In spite of these minor failings, the book is highly to be recommended and will furnish valuable reading and reference material to the student, the practitioner, and the investigator.

Samuel P. Bessman, M.D.

Diseases of the Endocrine Glands. 2nd Ed. By Louis J. Soffer, M.D., F.A.C.P., Clinical Professor of Medicine, State University of New York, College of Medicine, New York City; Attending Physician and Head of Endocrinology, The Mount Sinai Hospital, New York City; with J. Lester Gabrilove, M.D.,

F.A.C.P., Asst. Attending Physician and Member of the Endocrine Research Laboratory and Clinic, the Mount Sinai Hospital. 1032 pages; 15.5 × 24 cm. Lea & Febiger, Philadelphia. 1956. Price, $16.50.

In the past decade knowledge of the endocrine glands has advanced tremendously. Yet there are very few texts available which provide adequate and concise information for the student and physician interested in the field of endocrinology. Dr. Soffer's book fills a definite need in this respect. This second edition, produced with the assistance of Dr. J. L. Gabrilove and of Dr. A. R. Sohval who has written the section on the gonads, has been brought fully up to date and includes most of the recent advances made in the past five years since publication of the first edition.

The book is divided into five sections—The Hypophysis, The Adrenals, The Gonads, The Thyroid, and The Thymus and Parathyroids. A section on diabetes mellitus is not included for the justifiable reason given by the author that this extensive subject merits separate considerations which would greatly increase the length of this volume. Each section includes comprehensive treatment of the physiology of the gland, knowledge of which is requisite to the understanding of clinical disorders. There are several excellent illustrations of histological sections and of patients with typical lesions, together with numerous representative case reports. The book comprises a great deal of material. It is written in a lucid style adapted for easy reading and for quick reference. Where controversial issues are involved, all aspects of the argument are presented and all statements are well documented with an excellent bibliography. An appendix presents the commonly used methods of laboratory tests of endocrine function. This text is well recommended both for students of endocrinology and as a reference book for the practicing physician.

JOHN G. WISWELL, M.D.

Yellow Fever Vaccination (World Health Organization: Monograph Series No. 30). By SMITHBURN, DURIEUX, KOERBER, PENNA, DICK, COURTOIS, DE SOUZA MANSO, STUART and BONNEL. 238 pages; 16 × 24 cm. World Health Organization, Geneva; available in the U. S. A. from Columbia University Press, International Documents Service, New York. Price, $5.00.

During the past six years, the vast experience of many specialists in the control of yellow fever has been compiled in two volumes. The first of these, "Yellow Fever" edited by Dr. George K. Strode, was published in 1951. The second volume, World Health Organization Monograph No. 30 entitled "Yellow Fever Vaccination," has just been published. The more recent work, compiled by foremost authorities on the subject of immunization of man against yellow fever, has summarized concisely all of the available information on this aspect of yellow fever control.

Dr. K. C. Smithburn discusses the immunology of yellow fever as it relates specifically to vaccination and in addition considers the pertinent publications on this subject which have appeared since 1951. A comparison of active immunity following experimental infection and that induced by vaccination is made with appropriate examples. Several protection tests used to demonstrate immunity are described and the many variables in these tests such as age and breed of mice, route of inoculation and size of challenge inoculum are discussed. The value of these immunologic procedures in the estimation of population immunity, identification of illnesses and identification of viruses is emphasized.

General Durieux and Major Koerber describe in great detail the method of preparation and technic of administering Dakar vaccine as well as the immune response induced by this virus. For those who are not already familiar with publications on the use of the French neurotropic or Dakar mouse-brain vaccine in some

56 million vaccinations in French West and Equatorial Africa, this is a most valuable section.

A detailed discussion of the preparation of 17D chick-embryo vaccine and its administration in Brazil is given by Dr. H. A. Penna. Mass vaccination in Brazil during which 21 million individuals were inoculated with 17D vaccine is described by Dr. C. de Souza Manso. The recent studies of Drs. Dick and Hahn have clearly shown that a high percentage (93–97%) of non-immune individuals develops antibody following vaccination with 17D virus by scarification. As the efficacy of 17D vaccine (as measured by antibody production) administered by scarification appears to be comparable to that given by the subcutaneous route, the saving and ease of administration afforded by the former method suggest that this route of inoculation may be preferred for future work.

The results of experiments designed to estimate the time of appearance of antibody as well as the duration of immunity measured by the neutralization test following vaccination with 17D virus are reported by Dr. Courtois.

The problem of post-vaccination reactions is reviewed by Dr. G. Stuart. The accumulated evidence suggests that Dakar virus produces more post-vaccination reaction than does 17D virus. Of particular importance are the post-vaccination meningo-encephalitides which have occurred with both vaccines. Recent studies, however, indicate that reactions of all types have been nearly eliminated in the case of 17D vaccine by scarification. The occurrence of serious outbreaks of encephalitis following the use of Dakar vaccine in Costa Rica and Nigeria serves to emphasize the potential dangers of immunization with living neurotropic viruses.

Dr. Bonnel has outlined the international regulation of yellow fever vaccination in which vaccine centers and current requirements are given. Finally, this very valuable monograph is accompanied by a selected bibliography on yellow fever vaccination prepared by Dr. Bonnel.

The student of infectious diseases, be he clinician, virologist, epidemiologist or entomologist, is indeed fortunate that so many valuable lessons have been recorded in this one volume.

F. R. McCrumb

Neuropharmacology. Transactions of the First Conference, May 26, 27 and 28, 1954, Princeton, N. J. Edited by Harold A. Abramson, M.D. 210 pages; 16 × 24 cm. The Josiah Macy, Jr. Foundation, New York, N. Y. 1955. Price, $4.25.

The Macy Foundation has, for some years, done its best to encourage progress in biology and medicine through the support of various conferences. These discussion groups have been focused on areas in which either new ideas and pathways were necessary, or had already become apparent but need clarification, direction and attempts at integration with existing "fact" and theory. It was a logical consequence, then, to assume that the establishment of a series of conferences dealing with neuropharmacology would mean a new approach, and a fresh, provocative point of view.

Unfortunately, it is with great dismay that this reviewer must report that the first volume of neuropharmacological transactions makes his assumption invalid and his "logical consequence" illogical. The titles of the various discussion sections make it plain that the relationship of drug action to neural activity has been considered only from points of view previously expressed and discussed at length in other places. Some of these titles are: functional organization of the brain; the effects of pharmacological agents on the overall circulation and metabolism of the brain; ascending reticular system and anesthesia; and electrical activity of the brain in relation to anesthesia. It is clear that a great deal of data and concept slightly

redirected, or with the emphasis slightly reoriented, can be discussed by groups concerned with mechanisms of consciousness or of the nerve impulse or even of neuropharmacology. This general observation does not, of course, decrease the value or importance of the work involved any more than it overcomes the oft repeated superficialities and the absent new directions.

There is neither the space nor is there any particular value at this time in examining each part of the conference in detail. There is much useful information that will be of interest to many investigators working in any of several fields concerned with problems of the nervous system. Often throughout these presentations and discussions ancillary issues arise which are of great importance and merit serious consideration. One such instance can be found in the remarks of Dr. M. A. B. Brazier to the effect that electroencephalographers ". . . are always describing pen movement. Because they look alike, are they necessarily causally related?" Unfortunately, this type of problem is not followed up, so that it cannot accomplish what it should. This lack may or may not be a fault inherent in this type of discussion group. On the other hand, there is always the possibility that further consideration could have been stimulated by the chairman.

To this reviewer the most disappointing characteristics of the conference are two. First, is its complete neglect of the fundamental general physiological problems involved—the omission of physico-chemical data, concept and theory. Nowhere is there any awareness of the rôle of molecular structure, orientation and kinetics in the nerve cell membrane—a rôle which recent information would suggest is a vital part of any neuropharmacological mechanism. Second, is the absence of any real consideration of the relationship of chemicals and drugs to psychological problems and behavior (despite the fact that this is stressed in the introductory remarks). It is hoped that the future meetings of this group will be somewhat differently oriented and will accomplish more of the kind of integration and productive speculation which has made other such discussions so profitable.

R. G. GRENELL

Henry Ford Hospital International Symposium on Cardiovascular Surgery: Proceedings of the Symposium held at Henry Ford Hospital, Detroit, Michigan, March, 1955. Edited by CONRAD R. LAM, M.D., Surgeon-in-Charge, Division of Thoracic Surgery, Henry Ford Hospital. 543 pages; 16.5 × 25.5 cm. W. B. Saunders Co., Philadelphia. 1955. Price, $12.75.

Henry Ford Hospital (Detroit, Michigan) held an International Symposium devoted to cardiovascular surgery in March, 1955. This volume contains the proceedings of the meeting. The renowned participants—surgeons, physicians, radiologists, pathologists, and physiologists—came from several countries. Most of the papers were concerned with surgical technics, problems, and results. Some diagnostic methods were reviewed, and certain features of physiologic mechanisms which influence cardiovascular surgery were considered.

Internists interested in cardiology will appreciate the collection of such highly diversified material into one volume. The variety of surgical procedures available for various cardiovascular lesions should interest physicians who care for patients having these diseases. The need for careful study, by all available diagnostic technics, of patients with more complicated clinical problems was stressed. There was ample discussion about the flaws and risks of each surgical procedure. The difficulties in the evaluation of results in many cardiac patients were reviewed.

Sir Russell Brock, in an entertaining and stimulating Foreword, paid tribute to the men of many disciplines whose imaginations and coöperative efforts have contributed to the current status of cardiovascular surgery and physiology. This symposium exemplified the diversity of thought, spirit of coöperation, and critical analysis needed for further progress in a rapidly expanding field.

The presentations were lucid, and several points were clarified in the discussions. This book can be well recommended to interested physicians and surgeons.

J. E. C.

BOOKS RECENTLY RECEIVED

Books recently received are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

Adrenal Function in Infants and Children: A Symposium. Edited by LYTT I. GARDNER, M.D., Associate Professor, Department of Pediatrics, State University of New York, College of Medicine, Syracuse, New York. 221 pages; 22 × 14 cm. 1956. Grune & Stratton, New York. Price, $6.75.

Cardiovascular Innervation. By G. A. G. MITCHELL, O.B.E., T.D., M.B., Ch.M., D.Sc., Professor of Anatomy and Director of the Anatomical Laboratories in the University of Manchester, etc.; foreword by SIR GEOFFREY JEFFERSON, C.B.E., M.S., M.Ch., M.Sc., LL.D., F.R.C.P., F.R.C.S., F.R.C.S.I., F.R.F.P.S., F.A.C.S., F.R.S., Emeritus Professor of Neurological Surgery in the University of Manchester. 356 pages; 25.5 × 18 cm. 1956. The Williams & Wilkins Company, Baltimore. Price, $11.00.

Clinical Recognition and Management of Disturbances of Body Fluids. By JOHN H. BLAND, M.D., Associate Professor of Medicine, University of Vermont College of Medicine. 522 pages; 26 × 18 cm. 1956. W. B. Saunders Company, Philadelphia. Price, $11.50.

Collagen Diseases, Including Systemic Lupus Erythematosus, Polyarteritis, Dermatomyositis, Systemic Scleroderma, Thrombotic Thrombocytopenic Purpura. By JOHN H. TALBOTT, M.D., Professor of Medicine, The University of Buffalo School of Medicine, etc.; and R. MOLERES FERRANDIS, M.D., Training Fellow in Arthritis of the Western New York Chapter of the Arthritis and Rheumatism Foundation. 232 pages; 22.5 × 14 cm. 1956. Grune & Stratton, New York. Price, $6.50.

Derniers Aspects du Monde des Mycobactéries. By PAUL HAUDUROY. 92 pages; 25.5 × 17 cm. (paper-bound). 1955. Masson & Cie, Paris. Price, 750 fr.

Diseases of the Nervous System. 5th Ed. By SIR RUSSELL BRAIN, Bt., D.M. (Oxon.), F.R.C.P. (London), Physician to the London Hospital and to the Maida Vale Hospital for Nervous Diseases, etc. 996 pages; 22.5 × 14.5 cm. 1956. Oxford University Press, New York. Price, $10.50.

Electrocardiography: Fundamentals and Clinical Application. 2nd Ed. By LOUIS WOLFF, M.D., Visiting Physician, Consultant in Cardiology and Chief of the Electrocardiographic Laboratory, Beth Israel Hospital, etc. 342 pages; 25.5 × 16.5 cm. 1956. W. B. Saunders Company, Philadelphia. Price, $7.00.

The Flavonoids in Biology and Medicine: A Critical Review. Nutrition Monograph Series Number 2. By MAURICE E. SHILS, Sc.D., and ROBERT S. GOODHART, M.D. 101 pages; 23 × 15.5 cm. (paper-bound). 1956. The National Vitamin Foundation, Incorporated, New York. Price, $2.00.

Die Frühdiagnose des Uteruscarcinoms: Histologie, Kolposkopie, Kolpophotographie, Cytologie, Biochemische Methoden. By PROF. DR. MED. HANS LIMBURG. 334 pages; 21.5 × 15 cm. 1956. Georg Thieme Verlag, Stuttgart; in the U. S. A. and Canada: Intercontinental Medical Book Corporation, New York. Price, Ganzleinen DM 36.–

Gestation: Transactions of the Second Conference, March 8, 9, and 10, 1955, Princeton, N. J. Edited by CLAUDE A. VILLEE, Ph.D., Assistant Professor of Biological Chemistry, Department of Biological Chemistry, Harvard Medical School, Boston, Massachusetts. 262 pages; 24 × 15.5 cm. 1956. Sponsored by the Josiah Macy, Jr. Foundation, New York. Price, $5.00.

Gynecologic Cancer. 2nd Ed. By JAMES A. CORSCADEN, Ph.B., M.D., Professor Emeritus of Clinical Gynecology, College of Physicians and Surgeons, Columbia University, etc. 546 pages; 23.5 × 15.5 cm. 1956. The Williams & Wilkins Company, Baltimore. Price, $10.00.

Histopathologie du Foie: Le Diagnostic des Affections Hépatiques Étude Iconographique. By P. CAZAL. 207 pages; 32.5 × 25 cm. 1955. Masson et Cie, Paris. Price, Broché 4.000 fr.; Cartonné toile, 4.800 fr.

The Inquisitive Physician: The Life and Times of George Richards Minot, A.B., M.D., D.Sc. By FRANCIS M. RACKEMANN, A.B., M.D. 288 pages; 24 × 16 cm. 1956. Harvard University Press, Cambridge. Price, $5.00.

Interne Therapie der Organischen Herz- und Kreislauferkrankungen. Nauheimer Fortbildungs-Lehrgänge Bd. 21. Herausgegeben von Vereinigung der Bad Nauheimer Ärzte. 130 pages; 24.5 × 17 cm. (paper-bound). 1956. Verlag von Dr. Dietrich Steinkopff, Darmstadt. Price, Brosch. DM 13.–

Laboratory Tests in Common Use. By SOLOMON GARB, M.D., Assistant Professor of Clinical Pharmacology, Cornell University Medical College. 160 pages; 18.5 × 12.5 cm. (paper-bound). 1956. Springer Publishing Company, Inc., New York. Price, $2.00.

Les Néphrites Ascendantes. Monographies de la Société de Pathologie Rénale. By MME. TH. BERTRAND-FONTAINE and MM. R. COUVELAIRE, A. NENNA, CH. OBERLING, J. SCHNEIDER. 74 pages; 24.5 × 16 cm. (paper-bound). 1955. Masson & Cie, Paris. Price, 480 fr.

Neurochemistry. Progress in Neurobiology: I. Edited by SAUL R. KOREY, M.D., Professor of Neurology, Albert Einstein College of Medicine of Yeshiva University, New York, New York; and JOHN I. NURNBERGER, M.D., Research Associate, The Institute of Living, Hartford, Connecticut, etc.; with twenty-three contributors. 244 pages; 24 × 15.5 cm. 1956. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. Price, $6.75.

Précis d'Épidémiologie et Prophylaxie des Grandes Endémies Tropicales. 3d Ed. By V. REYNES; préface du Médecin-Général-INSPECTEUR VAUCEL. 418 pages; 21.5 × 16.5 cm. (paper-bound). 1955. Masson & Cie, Paris. Price, 2.800 fr.

Radium Therapy: Its Physical Aspects and Extensions with Radioactive Isotopes. 2nd Ed. By C. W. WILSON, M.Sc., Ph.D., F. Inst. P., Principal Physicist to the Westminster Hospital, London; foreword by SIR STANFORD CADE, K.B.E., C.B., D.Sc., F.R.C.S., M.R.C.P., F.F.R., Senior Surgeon, the Westminster Hospital, London. 286 pages; 24 × 15.5 cm. 1956. The Williams & Wilkins Company, Baltimore. Price, $7.50.

Textbook of Medical Physiology. By ARTHUR C. GUYTON, M.D., Professor and Chairman of the Department of Physiology and Biophysics, University of Mississippi School of Medicine. 1,030 pages; 26 × 18 cm. 1956. W. B. Saunders Company, Philadelphia. Price, $13.50.

COLLEGE NEWS NOTES

Summary Report of the Thirty-Seventh Annual Session of the College

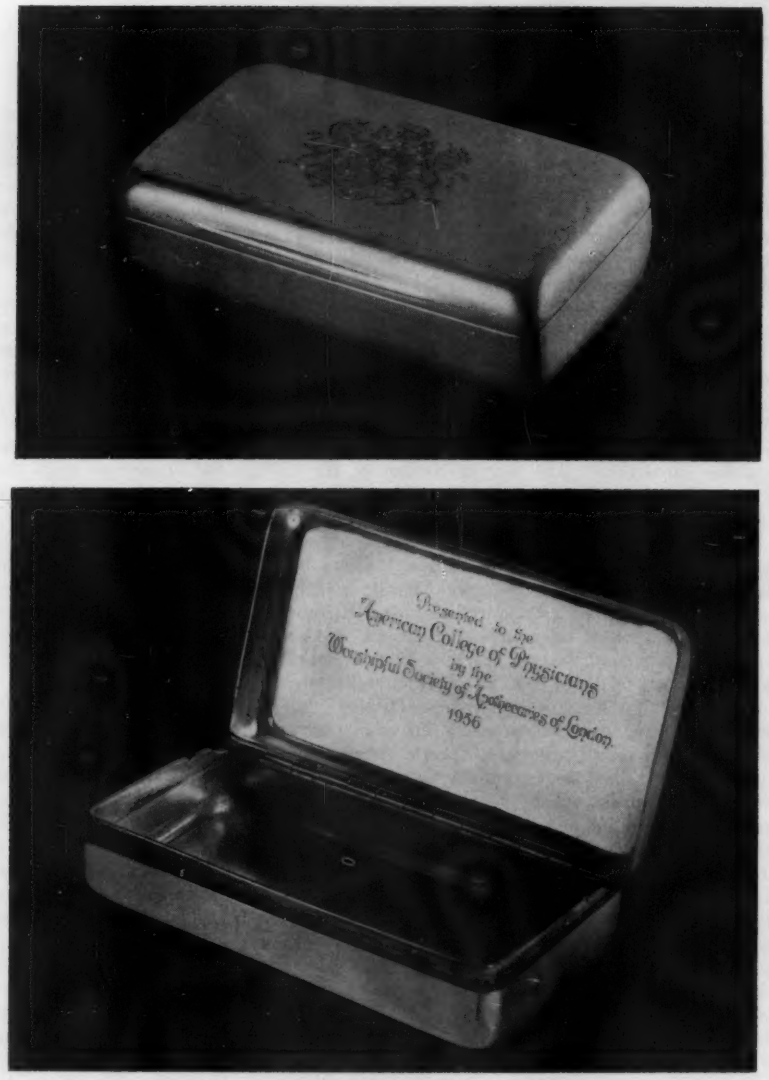
The Thirty-seventh Annual Session of the American College of Physicians, held at Los Angeles, Calif., under the Presidency of Dr. George F. Strong, of Vancouver, B. C., and the General Chairmanship of Dr. George C. Griffith, of Los Angeles, was by far the most largely attended meeting of the College ever held west of the Mississippi River. There were in attendance over 4,500 individuals. In addition to attendance from the United States and Canada, physicians were present from Australia, Cuba, Germany, Japan, Mexico, South Africa, Switzerland, Colombia, Venezuela, Hawaii and Puerto Rico.

The program, while following the pattern of College programs for the past several years, introduced some new features in the form of Clinical Biochemical Conferences and Hospital Clinics fully televised in color to the centrol auditorium. There was a certain newness to the program, in that many new names appeared as contributors and subjects were presented that had not been used frequently in the past. There was an exceptionally large and fine Technical Exhibit. A limited Scientific Exhibit, largely from the medical schools of the Rocky Mountain and West Coast area was introduced. The Annual Session of the College has become so large that it is necessary to offer optional program features, which run concurrently, thus to distribute the large number in attendance.

The Committee on Entertainment presented an exceptionally fine program for the diversion of the guests, including a Concert by the Los Angeles Philharmonic Orchestra, with the Roger Wagner Chorale and soloists, an evening at the Frank Sennes' Moulin Rouge, a Banquet at which Mr. Bob Hope was Master of Ceremonies and many Hollywood celebrities participated, and an exceptionally fine program for the visiting women. For the first time in the history of the College the Banquet was so popular that facilities were inadequate, and many were unable to obtain tickets.

For the first time in the College History, the Convocation was conducted in academic gowns, the College using an official gown and guests appearing in the gowns of their own institutions, several from foreign countries. In the Procession were the Officers and Regents of the College, the Governors of the College, candidates for special awards, official representatives of other societies, both domestic and foreign, the new Fellows to be inducted, Brower, Bowes and Thompson Traveling Scholars, A.C.P. Research Fellows and Latin-American Fellows; the Convocational Lecturer was Dr. Macdonald Critchley, F.R.C.P., of London, England, on whom an Honorary Fellowship was conferred; Doctors Arthur L. Bloomfield, of San Francisco, and Esmond R. Long, of Pedlar Mills, Va., on whom Masterships were conferred; Dr. John F. Enders, of Boston, Mass., on whom the Bruce Memorial Award in Preventive Medicine was conferred; Dr. Linus Pauling, of Pasadena, Calif., on whom the Phillips Memorial Award was conferred; Dr. Cyrus C. Sturgis, of Ann Arbor, Mich., on whom the Alfred Stengel Memorial Award was conferred; Dr. Herbert K. Detweiler, of Toronto, Ont., official representative of the Royal College of Physicians and Surgeons of Canada; Dr. Dwight H. Murray, of Napa, Calif., President-Elect, official representative of the American Medical Association; Dr. Gilbert J. Thomas, of Santa Monica, Calif., official representative of the American College of Surgeons, and Dr. John G. E. Hayden, of Sydney, Australia, official representative of the Royal Australasian College of Physicians.

At this Annual Session 259 new candidates were elected to Associateship, 127 Associates were advanced to Fellowship and 4 candidates were elected to Direct Fellowship. At the November, 1955, meeting of the Board of Regents, 295 candidates



Antique Silver Snuff Box (Circe 1800)
Presented to The American College of Physicians
By the Worshipful Society of Apothecaries of London
Through courtesy of Macdonald Critchley, M.D., F.R.C.P.

were elected to Associateship, 112 Associates were advanced to Fellowship and 2 candidates were elected to Direct Fellowship. Summarizing the year's elections, there were 245 candidates elected to Fellowship and 554 candidates elected to Associateship. All of those elected to Fellowship during the year were inducted, if present, at the Convocation.

At the Annual Business Meeting, Dr. George F. Strong retired as President and was elected to the Board of Regents for a term of three years. Dr. Walter L. Palmer, of Chicago, was inducted to the Presidency; Dr. Richard A. Kern, of Philadelphia, became President-Elect; Dr. Chester M. Jones, of Boston, became First Vice President; Dr. George H. Anderson, Spokane, became Second Vice President and Dr. Truman G. Schnabel, Sr., of Philadelphia, became Third Vice President. Reëlected to the Board of Regents were Dr. Fuller B. Bailey, of Salt Lake City, Dr. Eugene B. Ferris, of Atlanta, Dr. Philip S. Hench, of Rochester, and Dr. Chester S. Keefer, of Boston. Of the Governors of the College whose terms expired at this meeting and who were not eligible for reëlection, the following new Governors were elected for term expiring in 1959: Dr. John N. Compton, Little Rock, for ARKANSAS; Dr. Reinhold O. Goehl, Sr., of Grand Forks, for NORTH DAKOTA; Dr. Orlando B. Mayer, of Columbia, for SOUTH CAROLINA, Dr. Elbridge E. Johnston, of St. Johnsbury, for VERMONT, Dr. James W. Haviland, of Seattle, for WASHINGTON, and Dr. Carlos F. Cardenas, of Havana, for CUBA.

At the closing meeting of the Board of Regents, Dr. Wallace M. Yater, of Washington, D. C., was elected Secretary-General, and Dr. Robert Wilson, of Charleston, S. C., was appointed to the Board of Regents, to fill out the unexpired term of Dr. Yater, to 1957. The personnel of new Committees will be published in a succeeding issue of this Journal.

At the conclusion of the Annual Session in Los Angeles, a group of approximately 200 joined the Post-Convention Medical Cruise to Hawaii, where the Centennial Celebration of Medicine in Hawaii was conducted by the Hawaiian Medical Association, with meetings being attended not only by the local profession and members of the College, but by a number of other visiting physicians from other parts of the world and several non-members of the College from the United States. There was also arranged many entertainment features for members of the College, including a day on the Island of Kauai, sight-seeing trips on the Island of Oahu, a tour in the Commandant's barge of Pearl Harbor, during which President Strong placed a wreath on the sunken battleship U. S. S. Arizona, private parties and dinners, one given by Dr. Nils P. Larsen, College Governor for Hawaii.

The 1957 Annual Session will be held at Boston, Mass., April 8–12, under the Presidency of Dr. Walter L. Palmer, of Chicago, and the General Chairmanship of Dr. Richard P. Stetson, of Boston.

The 1958 Annual Session will be held at Atlantic City, N. J., April 28–May 2, under the Presidency of Dr. Richard A. Kern, of Philadelphia, and the General Chairmanship of Dr. James F. Gleason, of Atlantic City.

The Executive Secretary of the College Honored

At the Annual Business Meeting of the College at Los Angeles, Calif., on April 19, 1955, the Constitution and By-Laws of the College were amended, to empower the Regents to confer an Honorary Fellowship on a non-medical individual and without restrictions as to country of residence. Thereupon, an Honorary Fellowship was conferred upon Mr. Edward R. Loveland, who has been the Executive Secretary of the College for thirty years, since April 1, 1926. The President, in conferring the Honorary Fellowship, read the following citation from an illuminated parchment Certificate, the said Certificate being presented to Mr. Loveland:

Presidential Medal or Badge
Presented to The American College of Physicians
By Sir Russell Brain, President of the
Royal College of Physicians of London

"THE AMERICAN COLLEGE OF PHYSICIANS

"The Board of Regents of the American College of Physicians, in agreement with the wishes of the Membership of the College, has unanimously voted this certificate of

Honorary Fellowship

to

Edward R. Loveland

"As Executive Secretary of the College from 1926–1956; his ability and devotion have been outstanding. His services have been distinguished by his constant adherence to the highest traditions of the medical profession.

"During these years he has played an essential role in the advancement of the program of the College in the fields of Medical Education and Medical Science.

"In grateful appreciation the Board of Regents and the Membership have selected him at the Annual Session of 1956 in Los Angeles as the first and only Recipient, other than a physician, of such Honorary Fellowship in the history of the College."

New Life Members

The College acknowledges with pleasure the following Fellows as Life Members:

Dr. Harold E. Stadler ..... Indianapolis, Ind.
Dr. Arthur C. Corcoran ..... Cleveland, Ohio
Dr. Victor George deWolfe ..... Cleveland, Ohio
Dr. James S. Hewlett ..... Cleveland, Ohio

A.C.P. Postgraduate Courses, Autumn 1956

The Committee on Postgraduate Courses announces the following schedule for the autumn of 1956. In a few instances dates have not been established. One additional course, probably in electrocardiography, will be added. The Postgraduate Bulletin giving final dates and all details of each course will be published during the early summer.

This program is one of the primary methods by which the College encourages postgraduate study and through which the College extends its services to its Fellows and Associates. Where facilities are available these courses will be open to non-members with adequate preliminary training and experience.

All registrations must be filed with the Executive Secretary, American College of Physicians, 4200 Pine Street, Philadelphia 4, Pa. Fees, for members, $30.00 per week; non-members, $60.00 per week.

1. RECENT ADVANCES IN CARDIOVASCULAR DISEASE: Mt. Sinai Hospital, New York, N. Y.; Arthur M. Master, M.D., F.A.C.P., and Charles K. Friedberg, M.D., F.A.C.P., Co-directors. (October 8–12, 1956.)
2. INTERNAL MEDICINE: Vanderbilt University School of Medicine, Nashville, Tenn.; Rudolph H. Kampmeier, M.D., F.A.C.P., and Hugh J. Morgan, M.D., M.A.C.P., Co-directors. (October 15–19, 1956.)

3. CLINICAL NEUROLOGY: Jefferson Medical College of Philadelphia, Philadelphia, Pa.; Bernard J. Alpers, M.D., F.A.C.P., Director. (October 15–19, 1956.)
4. INTERNAL MEDICINE: University of Washington School of Medicine, Seattle, Wash.; Robert H. Williams, M.D., F.A.C.P., Director. (October 22–26, 1956.)
5. GASTRO-ENTEROLOGY: University of Pennsylvania Graduate School of Medicine, Philadelphia, Pa.; Henry L. Bockus, M.D., F.A.C.P., Director.
6. INTERNAL MEDICINE: University of Oklahoma School of Medicine, Oklahoma City, Okla.; Stewart G. Wolf, Jr., M.D., F.A.C.P., Director.
7. PATHOLOGIC PHYSIOLOGY OF THE BLOOD DYSCRASIAS: Washington University School of Medicine, St. Louis, Mo.; Carl V. Moore, M.D., F.A.C.P., William J. Harrington, M.D. (Associate), and Edward H. Reinhard, M.D. (Associate), Co-directors. (February 18–22, 1957.)

SCHEDULE OF A.C.P. COMING REGIONAL MEETINGS

Date	*Territory*	*Governor*	*Official Guest*
Sept. 7–8	NEW ENGLAND (Que., Me., Vt., N.H., Mass., Conn., R.I.), Burlington, Vt.	Elbridge E. Johnston	E. R. Loveland, Executive Secretary
Sept. 8	NORTH DAKOTA, Minot	Reinhold O. Goehl	Joseph D. McCarthy, M.D.
Sept. 29	WEST VIRGINIA, Charleston	Paul H. Revercomb	.....
Oct. 16	NEW MEXICO, Albuquerque	Robert Friedenberg	.....
Oct. 19	WESTERN NEW YORK, Albany	John H. Talbott	Walter L. Palmer, M.D., President
Oct. 27	MIDWEST (Minn., Wis., Iowa, Ill., Ind.), Minneapolis	Wesley W. Spink	Walter L. Palmer, M.D., President; E. R. Loveland, Executive Secretary
Nov. 7	NEW JERSEY, Newark	Edward C. Klein, Jr.	.....
Nov. 16–17	MONTANA-WYOMING, Great Falls, Montana	Harold W. Gregg	Walter L. Palmer, M.D., President
Nov. ?	SOUTHEASTERN (Ala., Ga., S.C., Fla., Cuba), Nassau, Bahama Islands	William C. Blake, Chmn.	.....
Dec. 1	KENTUCKY-TENNESSEE, Nashville	Rudolph H. Kampmeier	.....
Dec. 6	NORTH CAROLINA, Chapel Hill	Elbert L. Persons	Walter L. Palmer, M.D., President
1956 ?	MICHIGAN, Ann Arbor	H. Marvin Pollard	.....

EXAMINATIONS BY CERTIFYING BOARDS

The American Board of Internal Medicine, William A. Werrell, M.D., Executive Secretary-Treasurer, 1 W. Main St., Madison 3, Wis. Written Examinations Oct. 15. Oral Examinations: New York City, Sept. 21–25.

The American Board of Dermatology and Syphilology, B.M. Kesten, M.D., Executive Secretary, 1 Haven Ave., New York 32, N. Y. Written Examinations: Various centers, July 26. Oral Examinations: St. Louis, Oct. 12–15.

The American Board of Pediatrics, John McK. Mitchell, M.D., Executive Secretary, 6 Cushman Rd., Rosemont, Pa. Oral Examinations: New York City, Oct. 12–14; San Francisco, Calif., Dec. 7–9.

The American Board of Radiology, B. R. Kirklin, M.D., Executive Secretary, Kahler Hotel Bldg., Rochester, Minn. Examinations: Los Angeles, Sept. 30–Oct. 4.

American College of Physicians Vacation Announcement

The offices of the American College of Physicians will be essentially closed, except for emergency matters, from Friday evening, July 27, to Monday morning, August 13, to provide vacations for the office staff. In this manner, better service can be rendered to the membership than by having staggered vacations and a crippled staff all through the summer months.

College Library

A library known as the American College of Physicians Memorial Library of Publications by Members, is maintained at College Headquarters. Members frequently present autographed copies of their books to the College so that the Library has become a living memorial to those members.

The College considers it a distinct honor to receive autographed copies of books written by its members. The books are acknowledged in the Annals of Internal Medicine, catalogued and carefully preserved for posterity. The books may be referred to at any time at College Headquarters.

Cumulative Index of the Annals of Internal Medicine

The Cumulative Index of the first forty volumes of the Annals of Internal Medicine will be completed and ready for distribution during November, 1956. The work entailed in indexing the Journal for the past forty volumes exceeded the anticipations of the Editor, but the work has been completed and the volume is on the presses and will be concluded by or before the middle of November.

A broadside announcement to all those who have previously indicated a desire to subscribe will be sent in due course.

Meetings, A.C.P. Committee on Credentials

The next meeting of the Committee on Credentials of the American College of Physicians will be held Nov. 8–9, immediately preceding the meeting of the Board of Regents on Nov. 10–11.

Proposals of new members or candidates for action at this meeting must be received at College Headquarters 60 days in advance of these dates. Governors may require that proposals be in their hands 90 days before the meeting.

Submission of Titles for A.C.P. 1957 Session

The Committee on Educational Policy of the Board of Regents has suggested that the Fellows and Associates of the College be invited to submit titles and abstracts (not to exceed 200 words) of papers to be considered for the Annual Session of the American College of Physicians at Boston, Mass., April 8–12, 1957. Consequently, all Fellows and Associates are invited to submit titles and abstracts to the President, Dr. Walter L. Palmer, 950 E. 59th St., Chicago 37, Ill., prior to Oct. 1, 1956. Presumably, it will be possible to place on the program of the 1957 Session at Boston only a small portion of the papers submitted. It is hoped, however, that the plan will bring to light many subjects and speakers who might be overlooked, and also that some information will be afforded regarding current interests. Suggestions may thus arise for symposia, panel discussions, morning lectures, clinics, and the afternoon sessions.

Applications for 1957 Research Awards Now Being Accepted by The American Heart Association

Applications by research investigators for support of studies in or related to the cardiovascular field are now being accepted by the American Heart Association. The awards would be for the fiscal year beginning July 1, 1957. Application deadline for research fellowships and established investigatorships is Sept. 15, 1956. For grants-in-aid, applications must be made by Nov. 1, 1956. Awards are made in the following categories:

Established Investigatorships: Awarded for periods of up to five years, subject to annual review, in amounts ranging from $6,000 to $9,000 per annum, to scientists of proven ability who have developed in their careers to the point where they are independent investigators.

Research Fellowships: Awarded to young men and women with doctoral degrees for periods of one to two years to enable them to train as investigators under experienced supervision. Annual stipends range from $3,500 to $5,600.

Grants-in-Aid: Made to experienced investigators in varying amounts up to $10,000 to provide support for specified projects.

Further information and application forms are available from the Medical Director, American Heart Association, 44 E. 23rd St., New York 10, N. Y.

The Joint Commission on Accreditation of Hospitals

A recent report from the Joint Commission indicates that, of 6,000 hospitals in the United States eligible for accreditation, 3,102 are fully accredited and 528 hold provisional accreditation. Some eligible hospitals have not applied for visitation, and some that did apply could not be inspected because of time limitations.

The Joint Commission on Accreditation of Hospitals represents the American College of Physicians, the American College of Surgeons, the American Hospital Association, the American Medical Association, and the Canadian Medical Association.

Occupational Medicine Course

An eight-week comprehensive course in occupational medicine for physicians will be given at the Post-Graduate Medical School of New York University-Bellevue Medical Center from Sept. 10 through Nov. 2, 1956.

Subjects being offered are: organization and administration of an industrial medical department; preventive and constructive medicine in industry; occupational diseases; toxicology and industrial hygiene for the physician; biostatistics; communicable disease control and epidemiology. Opportunities will be provided for attendance at medical, surgical and clinico-pathological conferences during the course. Tuition: $350.

For further information and application address: Dean, N.Y.U. Post-Graduate Medical School, New York 16, N. Y.

The Public Health Service has announced a new procedure to expedite the processing of research grant applications for those requests which do not exceed $2,000 plus indirect costs and which do not ask support for more than one year. Such applications will be accepted and processed on receipt and are not therefore subject to the usual deadlines for submission prior to review. Council recommendations can be expected on these applications within one to four months from the time

of submission. These procedures do not apply for requests for supplements to existing grants.

Address all applications as well as request for forms or additional information, to the Division of Research Grants, National Institutes of Health, Bethesda 14, Md.

Dr. J. Murray Kinsman, F.A.C.P., Dean, Professor of Medicine and Chairman of the Department of the University of Louisville School of Medicine and Regent of the American College of Physicians, presented the Nu Sigma Nu Annual James J. Waring Lecture, April 12, at the University of Colorado School of Medicine. Dr. Kinsman's lecture was on "The Management of the Hypertensive Patient."

This lecture is presented annually by the University of Colorado Chapter of Nu Sigma Nu in honor of Dr. James J. Waring, Emeritus Professor of Medicine. Dr. Waring is a Master of the American College of Physicians and a former Vice-President.

The U.S. Atomic Energy Commission has just released an 817 page book entitled "Radioisotopes in Medicine." This book is the complete proceedings of a special course on the subject which was conducted by the Oak Ridge Institute of Nuclear Studies in September of 1953. Contents of the book include papers concerning availability and uses of isotopes, problems in radiation, radiation measurement and dosimetry, tumor localization, diagnostic and therapeutic uses of radioiodine, metabolic and vascular studies, isotopes in the study and treatment of hematologic disorders, therapy with radioactive colloids and therapy with external and implanted sources. Edited by Gould A. Andrews, Marshall Brucer and Elizabeth B. Anderson of the Oak Ridge Institute of Nuclear Studies Medical Division.

This book may be obtained from the Superintendent of Documents, U.S. Government Printing Office, Washington 25, D.C., at a cost of $5.50.

Dr. Esmond R. Long, M.A.C.P., of Pedlar Mills, Va., was guest lecturer at the National Naval Medical Center, Bethesda, Md., April 26. Dr. Long gave a paper on "History of the Chemotherapy of Tuberculosis." Dr. Long was formerly Director, Henry Phipps Institute at the University of Pennsylvania.

The Texas Diabetes Association at its annual meeting elected the following officers: Drs. Edwin L. Rippy, F.A.C.P., President; Hugo T. Engelhardt, Sr., F.A.C.P., President-Elect; Lang F. Holland, F.A.C.P., First Vice President; Jabez Galt, F.A.C.P., Second Vice President; Richard E. Nitschke (Associate), Secretary Treasurer.

Dr. Rafael Rodriguez-Molina, F.A.C.P., College Governor for Puerto Rico, has been designated as the official representative of the American College of Physicians to the Fourth International Congress on Internal Medicine at Madrid, Spain, September 19–23, 1956. Dr. Rodriguez-Molina will present a paper on the official scientific program of the Congress.

Captain Julian Love, (MC) USN, F.A.C.P., after twenty-nine years of service, retired from active duty in the Navy on June 30, 1956, and will be associated with the City of Hope Medical Center, Duarte, California, as Director of the Outpatient Services and Consultant in Internal Medicine. Captain Love's last assignment in the Navy was that as Commanding Officer of the U.S. Naval Hospital, Corona, California.

Dr. Harold L. Goldburgh, F.A.C.P., Philadelphia, is Associate Professor of Clinical Medicine at Jefferson Medical College of Philadelphia, having been advanced from Assistant Professor of Clinical Medicine. Those having copies of the 1955 Directory of the College are invited to enter this correction.

Dr. Mayer A. Green, F.A.C.P., Pittsburgh, Pa., served as Chairman of a Postgraduate course in Allergy under the auspices of the American College of Allergists, April 17, at New York City.

Dr. Green also presented a paper at the Allergy Session of the American Medical Association Convention, June 14, entitled "Allergy and the Generalist."

Dr. I. Selig Epstein (Associate), of Philadelphia, presented a paper entitled "A New Method for the Diagnosis of Bronchogenic Carcinoma" at the 47th Annual Meeting of the American Association for Cancer Research held at Atlantic City, N. J., on April 13.

The American College of Physicians at its 37th Annual Session at Los Angeles, endorsed the Hill-Kennedy Bill which proposes the founding of a National Library of Medicine at Washington, D.C., and directed the Secretary to communicate urgent recommendation for its passage.

Dr. George E. Burch, F.A.C.P., has recently accepted the appointment as Associate Editor of the American Heart Journal. Dr. Burch is Professor and Head of the Department of Medicine at Tulane University School of Medicine.

The Leukemia Society, Inc., formerly known as the Robert Roesler de Villiers Foundation, has established a research award in leukemia. Grants offered in 1956 will take into consideration requests covering more than one year. Applications may be made throughout the year, to be reviewed at the meetings of the selection committee on Sept. 1, 1956, and March 1, 1957; they should be received not later than Aug. 15, 1956, and Feb. 15, 1957.

Detailed information may be obtained by writing to the Leukemia Society, Inc., 67 Wall St., New York 5, N.Y.

Coming Events, 1956–57

Aug. 26–Sept. 1 International Congress of Haematology, Boston, Mass.; The Congress, c/o Harrison Ave. & Bennet St., Boston 11, Mass.

Sept. 10–14 American Congress of Physical Medicine and Rehabilitation, Atlantic City, N. J.; Dr. Frances Baker, Secretary, 1 Tilton Ave., San Mateo, Calif.

Sept. 25–28 American Roentgen Ray Society, Los Angeles, Calif.; Barton R. Young, Germantown Hospital, Philadelphia 44, Pa.

Sept. 28–29 American Medical Writers' Association, Chicago, Ill.; Harold Swanberg, Secretary, 510 Maine St., Quincy, Ill.

Oct. 1–5 International Congress on Medical Records, Shoreham Hotel, Washington, D.C.; Miss Doris Gleason, Executive Director, American Association of Medical Record Librarians, 510 N. Dearborn St., Chicago 10, Ill.

Oct. 6–13 College of American Pathologists, Chicago, Ill.; Arthur H. Dearing, Secretary, 203 No. Wabash Ave., Chicago 1, Ill.

Oct. 7–12 American Society of Clinical Pathologists, Chicago, Ill.; C. G. Culbertson, 1040 W. Michigan St., Indianapolis 6, Ind.

Oct. 8–11 American Academy of Pediatrics, New York, N. Y.; Dr. E. H. Christopherson, Secretary, 610 Church St., Evanston, Ill.

Oct. 9–15 World Medical Association, Havana, Cuba; Dr. Louis H. Bauer, Secretary-General, Coliseum Tower Office Bldg., 10 Columbus Circle, New York 19, N.Y.

Oct. 14 American College of Gastro-enterology, New York, N.Y.; Mr. Daniel Weiss, Secretary, 33 W. 60th St., New York 23, N.Y.

Oct. 26–31 American Heart Association, Cincinnati, Ohio; Irving B. Hexter, Secretary, 44 E. 23rd St., New York 10, N.Y.

Nov. 12–14 Association of American Medical Colleges, Colorado Springs, Colo.; Dean F. Smiley, Secretary, 185 No. Wabash Ave., Chicago 1, Ill.

Nov. 12–15 Southern Medical Association (Golden Anniversary Meeting), Washington, D.C.; Executive Secretary and Treasurer, Mr. V. O. Foster, Empire Bldg., Birmingham 3, Ala.

Nov. 12–16 American Public Health Association, Atlantic City, N.J.; R. M. Atwater, Secretary, 1790 Broadway, New York 19, N.Y.

Nov. 27–30 American Medical Association, Clinical Meeting, Seattle, Wash.; Dr. George F. Lull, Secretary, 535 N. Dearnborn St., Chicago 10, Ill.

Dec. 2–7 Radiological Society of North America, Chicago, Ill.; D. S. Childs, Secretary, 713 E. Genesee St., Syracuse 2, N.Y.

Dec. 8–13 American Academy of Dermatology and Syphilology, Chicago, Ill.; James R. Webster, Secretary, 55 E. Washington St., Chicago 2, Ill.

Foreign

July 22–28 International Congress of Radiology, Mexico, D.F., Mexico; Dr. Jose Noriega, Secretary-General, Tepic 126 (2e piso), Mexico 7, D.F., Mexico.

July 29–Aug. 5 International Physiological Congress, Brussels, Belgium; Prof. J. Reuse, Faculte de Medicine et de Pharmacie, 115 Boulevard de Waterloo, Brussels, Belgium.

Aug. 1–15 Pan American Tuberculosis Congress, Medellin and Bogota, Colombia, South America; General Secretary, 26 de Marzo 1065, Montevideo, Uruguay.

Aug. 12–18 World Federation for Mental Health, Munich, Germany; Secretariat, 19 Manchester St., London W.1, England.

Aug. 19–23 International Congress of Diseases of the Chest, Cologne, Germany; Mr. Murray Kornfeld, Executive Director, 112 E. Chestnut St., Chicago 11, Ill.

Aug. 20–24 International Congress of Physical Medicine, Copenhagen, Denmark; Dr. B. Strandberg, Honorable Secretary, Kobenhavns amts sygehus Gentofte, Dept. of Rheumatology and Physical Medicine, Hellerup, Denmark.

Sept. 10–14 International Congress of Dietetics, Congress Palace, Esposizione Universale Roma, Rome, Italy; Prof. E. Serianni, Secretary-General, Associazione Dietetica, Italiana, via dei Penitenzieri, N. 13, Rome, Italy.

Sept. 10–14 Second Congress, European Society of Cardiology, Stockholm, Sweden; Prof. K. E. Grewin, Sodersjukhuset, Stockholm, Sweden.

Sept. 10–15 International Congress Against Alcoholism, Istambul, Turkey; International contre l'Alcoolisme, Case Gare 49, Lausanne, Switzerland.

Sept. 12–15 European Congress of Allergology, Florence, Italy; Prof. Umberto Serafini, Secretary-General, Instituto de Patollogia Medica, Viale Morgagni, Florence, Italy.

Sept. 19–23 International Congress of Internal Medicine, Madrid, Spain; Dr. J. C. De Oya, Secretary, Hostaleza No. 90, Madrid, Spain.

Oct. 4–6 Association of Clinical Pathologists, London, England; Dr. W. H. McMenemey, Maida Vale Hospital for Nervous Diseases, London W. 9, England.

Oct. 21–27 Ibero Latin American Congress of Dermatology, Mexico, D.F., Mexico; Dr. Manuel Malacara, Centro Dermatologico Pascua, Calle Dr. Garciadiego 21, Mexico 7, D.F., Mexico, Secretario.

Jan. 3–6, 1957 Congress of International Union Against Tuberculosis, New Delhi, India; Secretariat, The Union, 66 Boulevard Saint-Michel, Paris 6e, France.

Excerpts from Annual Report, A.C.P. Group Insurance Plans

The following data are abstracted from the Annual Report of the Group Insurance Administrators of the American College of Physicians in connection with the College-sponsored Group Insurance Plans.

Health and Accident. As of the end of April, 1956, $575,000.00 in disability benefits were paid to College members insured under this Plan. Over 4,000 members are subscribers and the number is increasing each month. All new members have the privilege of subscribing within 60 days of their notification of election to the College and all are acceptable at least at minimum coverage, without health restrictions. Members who have failed to join the Plan during an "open period" may still subscribe thereto but are subject to satisfactory health records.

Professional Liability. This Plan has been in effect since January 1, 1953, and over 1,950 members are currently insured and receiving protection. To date, 41 notifications of claims or possible claims, with settlement payments of $10,621.22, have been filed. In addition, reserves totalling $17,433.50 have been set up for anticipated loss settlements of known claims. The Plan is growing continuously and every member of the College in clinical practice certainly cannot afford not to be protected against liability suit. The more members subscribing to the Plan the greater the benefits will be.

Dread Diseases. Over 1,900 members have subscribed to this coverage and over $9,000.00 in benefits have been paid as a result of disability arising from the Dread Diseases covered under this Plan. Additionally, $5,280.00 has been set up in reserve for continuing claims. One member, in particular, suffered an attack of poliomyelitis and at the time of this report has received over $5,000 in disability benefits. His premium was $8.00. Claims for poliomyelitis, encephalitis and scarlet fever have also been paid under family coverage of this Plan.

New Benefits Available. (1) The Board of Regents on the recommendation of the Committee on Insurance at Los Angeles approved a plan for continued coverage for Health and Accident of currently insured members after their protection under the original Health and Accident Group Plan terminates as a result of the attainment of age 70. The carrier, Educators Mutual Insurance Company, has agreed to a Plan of continued coverage up to age 75. This is a separate policy but the insured member should make application before his last policy carrying him through age 70 expires. All pertinent information regarding this new Plan will be forwarded to all members at the time they attain age 70. (2) Premiums have been reduced under the Dread Disease Plan. Members previously paying a $4.00 premium on an individual basis will in the future pay only $3.00; members who included their families with children under age 21, formerly paying $8.00, will in the future pay $6.00. All adult dependents will be charged an additional $3.00 premium. These reduced rates were effective as of the renewal premium due date of June 15, 1956. Furthermore, the carriers have added two additional diseases, Rocky Mountain Spotted Fever and Mumps in adults to the 11 dread diseases previously mentioned in this policy.

All correspondence concerning the A.C.P. Group Insurance Plans should be directed to the Group Insurance Administrators, 404 South 42nd St., Philadelphia 4, Pa.

Auditor's Report, Year Ending December 31, 1955

February 20, 1956

To the Board of Regents
American College of Physicians, Inc.
4200 Pine St.
Philadelphia 4, Pa.

Mr. E. R. Loveland, Executive Secretary

Dear Sir:

I have examined the accounts of the

American College of Physicians, Inc.

for the year ending December 31, 1955, and the accompanying statements, including the Balance Sheet at December 31, 1955, the analyses of the General Fund and the Endowment Fund and the Statement of Income Account for the calendar year 1955 are in accordance with the books of Account, and in my opinion present fairly the financial position at December 31, 1955 and the results of operations for the calendar year 1955, in conformity with generally accepted accounting principles applied on a basis consistent with that of preceding years, and subject to the following comments:

Cash: The Cash was properly accounted for, was confirmed by direct correspondence with the following depositories, and the Petty Cash verified:

Girard Trust Corn Exchange Bank, Philadelphia	$101,035.23
Provident Trust Co., Philadelphia	29,250.32
Royal Bank of Canada, Montreal	9,820.99
Petty Cash	250.00
	$140,356.54

Accounts Receivable: The Accounts Receivable were examined and found to be less than one year old and appear to be collectible. The detailed accounts receivable were in agreement with the control account. No requests for confirmation of the accounts were mailed.

Investments: The securities were accounted for by direct correspondence and the income for the period under review was verified. The investment transactions are recorded properly in the general books of account and in the Investment Ledger, which is in agreement with the investment accounts of the General Ledger.

General: The changes in the amount of the ENDOWMENT FUND and the GENERAL FUND during the year 1955 are as follows:

	Balance Jan. 1, 1955	Balance Dec. 31, 1955	Increase
Endowment Fund	$ 441,215.45	$ 464,657.87	$ 23,442.42
James D. Bruce Fund	10,000.00	10,000.00	
A. Blaine Brower Fund	20,000.00	20,100.00	100.00
General Fund	722,917.99	793,372.80	70,454.81
Restricted Funds	1,581.72	1,810.67	228.95
Willard O. Thompson Fund	3,563.85	10,341.58	6,777.73
	$1,199,279.01	$1,300,282.92	$101,003.91

The Executive Secretary has analyzed the income of the ANNALS OF INTERNAL MEDICINE according to Volume, so that the income and expenses are stated according to the year of publication, with the exception of Volumes of prior years, which are closed out and not carried in an inventory account, with the sales properly credited to the General Fund according to the date of sale.

General Comments: The prepaid insurance at December 31, 1955 was not set up as a deferred expense; the other deferred and accrued items were verified; the charges to the Furniture and Equipment Accounts represent proper additions to the account, and the allowances for depreciation appear to be adequate. A depreciation reserve account has been set up for the Headquarters Building in accordance with the action of the Board of Regents at the meeting of December 12, 1937, which provided that depreciation on the Building should be taken into account at the rate of $1,000.00 per year and increased in 1949 to $2,000.00. A depreciation reserve account has been set up for 404–12 S. 42nd Street at the rate of $500.00 per year. The footings and extensions of the inventory were verified.

All ascertainable liabilities have been included in the Balance Sheet.

All recorded receipts from dues, initiation fees, exhibits, advertising, sales of publications, etc., were properly deposited in banks and all disbursements, as indicated on the vouchers, cancelled checks and bank statements were properly recorded in the books of account.

Respectfully submitted,

(Signed) DAVID ROBIN, *Auditor*

American College of Physicians, Inc.

Balance Sheet, December 31, 1955

General Fund

Assets		
Current:		
Cash in Banks and on Hand		$136,348.39
Accounts Receivable		16,399.95
American Air Lines		425.00
Inventory of Keys, Pledges and Frames		1,127.72
Accrued Income on Endowment Fund Investments		2,840.79
Accrued Income on General Fund Investments		1,956.81
Investments at Book Value		658,125.70
Insurance Deposit		555.00
		$817,779.36
Deferred:		
Expenses, 37th Annual Session	$ 9,913.45	
1955 Directory	4,498.58	
Advertising, Volume 44	40.37	14,452.40
Fixed:		
College Headquarters:		
Real Estate	$112,882.32	
Less Depreciation	26,000.00	86,882.32
Furniture and Equipment, at cost	$ 27,244.35	
Less Depreciation	12,522.34	14,722.01
404–12 S. 42nd Street:		
Real Estate	$ 14,144.72	
Less Depreciation	500.00	13,644.72
		$947,480.81

Liabilities			
Accounts Payable			$ 170.65
Deferred Income:			
Advance Subscriptions, Annals of Internal Medicine, Volume 44 to 50			71,260.81
1956 Exhibits, paid in advance			28,331.47
1955 Directory, paid in advance			10,378.82
Restricted Funds:			
Income on James D. Bruce Fund Investments			498.12
Income on A. Blaine Brower Fund Investments			1,158.60
Income on Willard O. Thompson Traveling Scholarship Fund			153.95
Elizabeth Archbold Bowes Traveling Scholarships		800.00	
Charles F. Martin Fund		2,500.00	
Mead Johnson Postgraduate Scholarship Fund		9,000.00	
Portrait-Photo Fund		660.09	
Alabama Regional Meeting		70.83	
Southeastern Regional Meeting		149.67	
1955–56 Reserve Fellowship Fund		12,675.00	25,855.59
Residency Revolving Loan Fund		20,000.00	
Dr. Emerson Emory	1,000.00		
Dr. Robert P. Hudson	1,000.00		
Dr. Traverse Robbins	1,000.00		
Dr. Paul J. Rosch	700.00	3,700.00	16,300.00
Total Current Liabilities and Funds			$154,108.01
General Fund, as annexed			793,372.80
			$947,480.81

Endowment Fund

Assets	
Current:	
Cash	$ 4,008.15
Investments at Book Value	501,091.30
Accrued Income on Investments	2,840.79
	$507,940.24

Liabilities	
Current:	
Endowment Fund Principal	$464,657.87
Accrued Income, Due to General Fund	2,840.79
James D. Bruce Fund	10,000.00
A. Blaine Brower Fund	20,100.00
Willard O. Thompson Traveling Scholarship Fund	10,341.58
	$507,940.24

Summary of Operations for the Calendar Year 1955

Income:			
Annual Dues		$ 81,716.81	
Initiation Fees		15,735.00	
Subscriptions, Annals of Internal Medicine		159,203.56	
Advertising, Annals of Internal Medicine		98,508.56	
Income from Investments, General Fund (including Accrued)		34,233.28	
Income from Investments, Endowment Fund (including Accrued)		21,139.43	
Dividend on Perpetual Insurance Deposit		60.00	
Income on Sale of "Annals" Volume Files		373.67	
Postgraduate Courses (Balance)		5,349.64	
Profit on Sale or Maturity of Securities, General Fund		4,137.82	
Profit on Equipment Traded In		80.00	
Interest on Time Deposits		197.55	
Rent, 404–12 S. 42nd Street		1,350.00	
Thirty-sixth Annual Session:			
Exhibits	$39,189.25		
1955 Banquet	258.17		
Guest Fees	7,880.00	47,327.42	
Total Income			$469,412.74
Expenses:			
Salaries		$ 97,179.79	
Communications		15,587.81	
Office Supplies and Stationery		3,540.97	
Printing		140,587.58	
Maintenance		432.93	
Traveling Expenses		20,392.55	
Editorial Assistance		1,430.00	
Cumulative Index		1,898.66	
Miscellaneous		3,620.98	
College Headquarters, Maintenance, Taxes, Insurance, etc.		5,743.93	
Depreciation on College Headquarters Building		2,000.00	
Depreciation on 404–12 S. 42nd Street		500.00	
Depreciation on Furniture and Equipment		2,974.20	
Keys, Pledges and Frames		224.42	
Regional Meetings		5,950.04	
John Phillips Memorial Award		337.50	
Investment Counsel Service and Security Custodian's Fee		1,315.00	
Employees' Pension Fund		6,896.95	
Advertising Discount		2,172.73	
Loss on Sale or Maturity of Securities, General Fund		1,348.93	
Joint Commission on Accreditation of Hospitals		16,681.50	
Collection and Exchange		41.45	
Interlingua Translations		500.20	
Thirty-sixth Annual Session—Special Expenses:			
Committee on Panel Discussions	$ 152.43		
Committee on Publicity	836.18		
Committee on Ladies' Entertainment	554.31		
Convocation	1,453.64		
Regents-Governors Dinner	1,215.00		
Ladies' Subscription Dinner	154.82		
Registration	909.00		
Rent	3,055.00		
Clinic Expenses	12.50		
Projection Service	1,269.00		
Rental of Equipment and Draperies	3,915.24		
College Booth Expenses	103.44		
Public Address System	468.50		
Clinical Pathological Conferences	6.00		
Reception and Dinner for New Members	2,449.33	16,554.39	
404–12 S. 42nd Street:			
Maintenance	$ 900.68		
Heat, Light, Gas and Water	19.64		
Taxes	515.10	1,435.42	
Total Expenses			$349,347.93
Net Income for 1955 Credited to General Fund			$120,064.81

INVESTMENTS

BONDS

At December 31, 1955

Par Value	*Bonds*	*Funds*	
		Endowment	*General*
$15,000	Allied Chemical & Dye Corp., Deb. 3½'s, 1978	$ 14,850.00	
10,000	Allied Chemical & Dye Corp., Deb. 3½'s, 1978		$ 9,962.50
14,000	Aluminum Co. of Canada, 3⅞'s, 1970		14,297.50
12,000	American Gas & Elec. Co., Deb., 3⅜'s, 1977	12,270.00	
9,000	American Tobacco Co., 3's, 1969	9,415.24	
14,000	American Tobacco Co. 3¼'s, 1977	14,087.50	
10,000	Arkansas Power & Light Co., 1st, 3½'s, 1982		10,367.00
15,000	Baltimore & Ohio Equip. Trusts, 3⅛'s, 1962		14,999.85
10,000	Carolina Clinchfield & Ohio Rwy. Co., 1st Mort. 4's, "A", 1965	9,465.70	
10,000	Chesapeake & Ohio Rwy. Equip. Trust Certs., 2⅞'s, 1965		9,854.18
12,500	Columbus Gas System, Deb. 3⅜'s, "C", 1977		12,500.00
2,500	Columbus Gas System, Deb. 3⅜'s, "C", 1977	2,500.00	
10,000	Connecting Rwy. Co., 1st, 3⅛'s, "A", 1976	9,600.00	
10,000	Connecting Rwy. Co., 1st, 3⅛'s, "A", 1976		8,925.00
6,000	Consolidated Edison Co. of New York, 3's, 1981	5,970.00	
25,000	General Motors Acceptance Corp., Deb., 3⅞'s, 1961	25,593.75	
10,000	General Motors Corp., Deb., 3¼'s, 25 yr., 1979	10,162.50	
20,000	Hydro Electric Power Commission of Ontario, Can., 3½'s, 1979	20,675.00	
15,000	New York Central Railroad Second Equip. Trust Cert., 3⅜'s, 1965		14,794.13
5,000	Oregon-Washington RR & Nav. Co., Ref. 3's, "A", 1960	5,300.00	
4,000	Oregon-Washington RR & Nav. Co., Ref. 3's, "A", 1960		4,240.00
20,000	Pennsylvania RR Equip. Trust Cert., 2½'s, 1961		19,700.00
15,000	Pittsburgh & Lake Erie RR, Equip. Trust Certs., 3's, 1964		14,723.04
10,000	Reading Co., Equip. Trust Certs., "U", 3½'s, 1963		9,999.90
10,000	Service Pipe Line Co., Deb., 3.20's, 1982	10,025.00	
10,000	Seaboard Airline Equip. Trusts, 2⅞'s, "L", 1966		9,746.80
15,000	St. Louis, San Francisco RR Co., Equip. Trusts, 2⅞'s, 1962		14,935.53
10,000	Texas & New Orleans RR Co., 1st & Ref., 3¼'s, "B", 1970	10,458.60	
12,000	U. S. Treasury Bonds, 2½'s, "G", March 1, 1957		12,000.00
10,000	U. S. Treasury Bonds, 2½'s, "G", March 1, 1957	10,000.00	
16,000	U. S. Treasury Bonds, 2½'s, "G", July 1, 1957	16,000.00	
7,000	U. S. Treasury Bonds, 2½'s, "G", February, 1958	7,000.00	
10,000	U. S. Treasury Bonds, 2½'s, "G", March 1, 1959	10,000.00	
6,000	U. S. Treasury Bonds, 2½'s, "G", July 1, 1959	6,000.00	
5,000	U. S. Treasury Bonds, 2½'s, "G", July 1, 1957		5,000.00
2,500	U. S. Treasury Bonds, 2½'s, "G", March 1, 1960	2,500.00	
2,500	U. S. Treasury Bonds, 2½'s, "G", January 1, 1961	2,500.00	
2,500	U. S. Treasury Bonds, 2½'s, "G", January 1, 1962	2,500.00	
2,500	U. S. Treasury Bonds, 2½'s, "G", June 1, 1962	2,500.00	
14,000	U. S. Treasury Bonds, Series "K", September 1, 1966	14,000.00	
20,000	U. S. Treasury Bonds, Series "K", December 1, 1966		20,000.00
12,500	U. S. Treasury Bonds, Series "K", January 1, 1967	12,500.00	
10,000	U. S. Treasury Bonds, Series "K", June 1, 1967		10,000.00
9,000	West Penn Electric Co., S.F., Coll. Tr., 3½'s, 1974	9,541.37	
	Total Bonds	$255,414.66	$216,045.43

INVESTMENTS

STOCKS

At December 31, 1955

Shares	*Stocks*	*Funds* — *Endowment*	*General*
157	Allied Chemical & Dye Corp., Common		$ 10,648.77
219	American Gas & Electric Co., Common	$ 4,035.03	
344	American Gas & Electric Co., Common		6,403.09
100	American Smelting & Refining Co., 7%, Pfd.	18,867.80	
300	Armstrong Cork Co.		8,868.93
160	Atchison, Topeka & Santa Fe RR.	9,770.74	
40	Atchison, Topeka & Santa Fe RR.		2,442.69
519	Atlantic City Electric Company, Common		6,488.66
174	Atlantic City Electric Company, Common	1,655.75	
100	Bethlehem Steel, 7%, Pfd.	16,825.75	
260	Campbell Soup Co., Common	10,330.06	
15	Campbell Soup Co., Common		595.97
125	Chase Manhattan Bank of New York, Common		4,550.00
178	Chase Manhattan Bank of New York, Common	5,039.67	
210	Commonwealth Edison Corp., Common	5,596.38	
210	Commonwealth Edison Corp., Common		7,593.24
100	Consumers Power Co., 4½'s Cum. Pfd.		11,287.50
300	Consolidated Edison Co. of New York		9,979.85
75	Continental Insurance Co. of New York, Common		3,445.00
50	Continental Insurance Co. of New York, Common	2,375.09	
300	Dow Chemical Co., Common		16,684.07
200	E. I. du Pont de Nemours, Common		8,714.85
134	Fidelity-Phoenix Fire Insurance Co., Common	6,124.94	
261	First Pennsylvania Banking & Trust Co.		9,066.56
70	First Pennsylvania Banking & Trust Co.	2,883.27	
300	General Electric Co., Common		3,571.78
300	General Electric Co., Common	3,780.96	
300	General Motors Corp., Common		3,594.53
180	General Motors Corp., Common	2,272.73	
200	B. F. Goodrich Tire Co., Common		7,830.39
300	Guaranty Trust Co. of New York, Common		19,890.20
351	Gulf Oil Corp., Common		11,846.67
288	Insurance Company of North America, Common	10,335.25	
50	International Harvester Co., 7%, Pfd.	8,169.00	
200	International Nickel Co. of Canada, Ltd., Common		6,605.79
243	International Paper Co., Common		9,261.50
50	Kaiser Aluminum & Chemical Co., 4.75 Cum. Pfd.	2,638.56	
350	Kaiser Aluminum & Chemical Co., 4.75 Cum. Pfd.		18,434.25
200	Kennecott Copper Corp., Common		10,918.21
100	Mead Corp., 4¼'s, Cum. Pfd.	9,796.05	
100	Mead Corp., 4¼'s, Cum. Pfd.		9,308.25
200	Mellon National Bank & Trust Co.		17,075.00
425	Middle South Utilities, Inc.	8,209.41	
375	Middle South Utilities, Inc., Common		8,192.35
206	Monsanto Chemical Co.		8,556.66
153	Monsanto Chemical Co., Common	5,056.95	
208	National City Bank of New York	7,989.85	
193	National City Bank of New York		8,844.29
400	New York State Electric & Gas Company		9,816.02
50	Niagara Mohawk Power Corp., 3.90% Pfd.		5,067.50
200	Niagara Mohawk Power Corp., Common		4,969.92
100	Niagara Mohawk Power Corp., 3.60% Pfd.	10,185.00	
300	Niagara Mohawk Power Corp., Common	6,625.67	
300	Ohio Edison Co., Common		13,010.25
200	Owens-Illinois Glass Co., Common		9,845.45
100	Owens-Illinois Glass Co., Common	5,364.40	
400	Pacific Gas & Electric Co., 6%, Pfd.		13,557.14
130	Pacific Gas & Electric Co., 6%, Pfd.	4,907.09	
200	Panhandle Eastern Pipe Line Co., 4% Cum. Pfd.	20,271.43	

INVESTMENTS—*Continued*

STOCKS

Shares	*Stocks*	*Funds*	
		Endowment	*General*
110	Pennsylvania Power & Light Co., Common	3,874.75	
340	Pennsylvania Power & Light Co., Common		11,456.43
136	Philadelphia Electric Co., Common		4,046.50
320	Philadelphia Electric Co., 1.00 Div., Pref. Common	7,791.13	
200	Phillips Petroleum Corp., Common		5,286.27
210	Pittsburgh Plate Glass Co., Common		10,805.93
300	Scott Paper Co., Common		10,547.48
100	Sherwin-Williams Co., Common		9,288.28
200	Southern California Edison Co., 4.23%, Cum. Pfd.		5,180.62
300	Southern California Edison Co., Common		15,308.43
400	Standard Oil Co. of New Jersey, Common		10,964.16
100	Tennessee Gas Transmission Co., 4.60%, Cum. Pfd.	10,924.64	
200	Tennessee Gas Transmission Co., 4.60%, Cum. Pfd.		19,680.70
400	Texas Company, Common	12,382.11	
200	Tide Water Associated Oil, 1.20 Cum. Pfd.		5,558.15
300	Transamerica Corp.		12,858.75
225	Union Carbide & Carbon Co.	6,146.98	
75	Union Carbide & Carbon Co.		3,019.88
290	U. S. Fidelity & Guaranty Co., (Md.)		11,113.36
100	U. S. Steel Corp., 7%, Cum. Pfd.	15,450.20	
	Total Stocks	$245,676.64	$442,080.27

Total Investments

	Endowment Fund	*General Fund*	*Total*
Bonds	$255,414.66	$216,045.43	$ 471,460.09
Stocks	245,676.64	442,080.27	687,756.91
	$501,091.30	$658,125.70	$1,159,217.00

OBITUARIES

RECENT DEATHS OF A.C.P. MEMBERS

The College records with sorrow the deaths of the following members. Their obituaries will appear later in these columns.

Dr. John Peters, F.A.C.P., Oak Park, Ill., Jan. 30, 1956
Dr. Lyell Cary Kinney, F.A.C.P., Escondido, Calif., February 1, 1956
Dr. Charles Joseph Bartlett, F.A.C.P., New Haven, Conn., March 6, 1956
Dr. James Henry Quinn, F.A.C.P., Springfield, Mass., March 8, 1956
Dr. James Ivan Mooney, F.A.C.P., Rochester, N. Y., March 28, 1956
Dr. Henry A. Reisman, F.A.C.P., Higganum, Conn., March 30, 1956
Dr. William Warner Watkins, F.A.C.P., Phoenix, Ariz., April 10, 1956
Dr. Harry Allison Alexander, F.A.C.P., Boulder, Colo., April 15, 1956
Brig. Gen. Henry Church Pillsbury, (MC), USA Ret'd, F.A.C.P., Ross, Calif., Date Unknown

DR. LOWELL ASHTON ERF

Dr. Lowell Ashton Erf, F.A.C.P., died in Philadelphia on January 30, 1956. He was born in Columbus, Ohio, March 17, 1908. He received both his B.S. and M.D. degrees from Ohio State University, graduating in Medicine in 1931. After spending one year as an intern in the White Cross Hospital in Columbus, he returned to the campus as the University's first medical and surgical research resident. Having found that his great interest lay in the field of hematology, he accepted the position of Assistant Hematologist to the Mount Sinai Hospital in New York City in 1934 and then became Hematologist to the May Research Institute for Hematology of the Jewish Hospital in Cincinnati, Ohio, in 1936. He returned to New York City where he became associated with the Rockefeller Institute from 1937 to 1939. He then became a research associate at the Crocker Radiation Laboratory at the University of California where he remained until 1941.

From 1941 until his untimely death, Dr. Erf was a very important member of the faculty of the Jefferson Medical College of Philadelphia. He originally joined this institution as Assistant Director of the Charlotte Drake Cardeza Foundation; in 1946, he became Assistant Professor in Medicine.

Dr. Erf belonged to many local and national societies. He became a Fellow of the American College of Physicians in 1944.

Dr. Erf contributed numerous articles to the medical literature. It should be remembered that he did outstanding pioneer work while he was a member of the faculty of the University of California when, in 1939, he administered radioisotopes to human subjects for the first time in the treatment of such diseases as chronic leukemia.

The death of a physician at the age of forty-seven years with the accomplishments and promise of Dr. Erf is a great loss, not only to his colleagues in Philadelphia but also to medicine everywhere.

The College extends its sympathy to Dr. Erf's wife, Evelyn D. Erf of Philadelphia.

THOMAS M. MCMILLAN, M.D., F.A.C.P.,
Governor for Eastern Pennsylvania, A.C.P.

DR. MALCOLM THOMAS MacEACHERN

Dr. Malcolm T. MacEachern, F.A.C.P., died February 3, 1956, in his seventy-fifth year at his home in Chicago. "Doctor Mac," of the hospital world, had been in failing health for some time but was at work in his home on the day of his death.

Dr. MacEachern was born in Argle, Ont., Canada, Aug. 27, 1881. He received his M.D. degree from McGill University in 1910. He was an interne at the Royal Victoria Hospital, Montreal in 1910. From 1913 until 1922 he was the General Superintendent of the General Hospital at Vancouver, B.C., Canada.

In 1923 he was appointed Associate Director and Director of Hospital Activities at the American College of Surgeons in Chicago. It was here, in the American College of Surgeons, that Dr. MacEachern started his pioneer work in elevating the standards of hospital care, not only in North America but in many foreign countries. This was the beginning of hospital accreditation and Dr. MacEachern's contributions to this field are many and notable.

In 1943 he founded the course in hospital administration at Northwestern University. He was professor and honorary Director at the time of his death.

In 1949 Dr. MacEachern became Director of the American College of Surgeons and retired as Director Emeritus in 1950. He joined the American Hospital Association as its director of professional relations in 1951.

Dr. MacEachern has probably visited, advised and inspected more hospitals than any man who has ever lived. He was often referred to as "Mr. Hospital," and rightly so.

Out of his vast experience in hospital organization in 1935 he wrote his textbook, "Hospital Organization and Management"—the outstanding text in its field. He was one of the key men in the organization of the American College of Hospital Administrators.

During his lifetime he was honored by many American and Foreign hospital organizations and governments. There seem to be no end of citations, awards of merit, plaques, keys and other honors. He became a Fellow of the American College of Physicians in 1933. He was President of the Chicago Medical Society in 1946 and 1947. Honorary degrees: Sc.D., Marquette University, 1926; LL.D., McGill University, 1950.

It was an inspiring experience to see the wonderful rapport between Dr. MacEachern and his individual students in his course in hospital administration at Northwestern University. He was stimulating and inspiring and at the same time warm and friendly. His students came from all over the globe.

He was courageous, lovable, intensely interested in his fellow men and generously self-sacrificing. His vitality shone brightly to the end of his life. His sparkling mind, his greatest gift, retained its lustre to his last hours. His was a great life.

He is survived by his wife, Fanny Brandon MacEachern, 3459 Simpson Street, Montreal 25, Quebec, Canada.

HOWARD WAKEFIELD, M.D., F.A.C.P.,
Governor for Northern Illinois, A.C.P.

DR. JOHN EDWARD McCORVIE

John Edward McCorvie died at Peoria, Ill. on Oct. 29, 1955, of coronary occlusion. He was born May 2, 1892 at Chatham, Ont., Can. He received his B.S. and M.D. degrees from the University of Toronto and the University of Toronto Faculty of Medicine—the latter in 1914, after which he spent one year as a Fellow in Pharmacology at his alma mater. In 1915 he interned at the Hospital for Sick Children, Toronto. During World War I, he served as a Captain with the Canadian

Army Medical Corps. From 1920 through 1923 he was a Fellow in Medicine at the Mayo Foundation, after which he located at Peoria. He has been a member of the staff of St. Francis Hospital since 1924 and served at one time as its President and its Chief of Medical Service. In addition to his affiliation with St. Francis Hospital, he was a member of the Associate Staff of the Methodist Hospital of Central Illinois, a consultant in Internal Medicine to the Peoria Municipal Tuberculosis Sanitarium, a Director of the Peoria County Tuberculosis Association and of the Central Illinois Hospital Association. During World War II he served as a member of Peoria's Selective Service Board No. II. He was a member of the council of the Peoria Medical Society; a member of the Illinois State Medical Society, the American Medical Association and the American Heart Association. He became a Fellow of the American College of Physicians in 1942.

Dr. McCorvie is survived by his widow, Mrs. Ahna McCorvie, of 303 Bigelow Avenue, Peoria 5, Ill., and a son, Neal, a junior at Princeton, and a daughter, Lynn, a junior at Peoria High School.

Dr. McCorvie's many friends and patients mourn his death at this time.

CHARLES H. DRENCKHAHN, M.D., F.A.C.P.,
Governor for Southern Illinois, A.C.P.

DR. CLOVIS LITLE McKIBBEN

Clovis Litle McKibben died at Ontario, Calif., on January 21, 1956, at the age of 58, of a nervous disorder. He was born March 17, 1897, at Zaleski, Ohio. He received his A.B. in 1921 from Ohio University and his M.D. from the University of Cincinnati College of Medicine in 1924. He then spent his internship at St. Vincent's Hospital in Toledo, Ohio, 1924–25, where he later became a member of the Junior Staff, Instructor to Nurses and interns, and a member of the Senior Attending Staff. He retired from active practice in May, 1942, because of ill health. He then moved to Ontario, Calif. While in California, he did not engage in the practice of medicine but became very active in ranching and worked faithfully in the Presbyterian Church where he was an Elder. Although he did not practice in this area, he was held in the highest esteem by all the physicians who knew him. He was a member of the Academy of Medicine of Toledo and Lucas Counties, and former Chairman of the Section on Medicine of the Ohio State Medical Association. He was a member of the Lambda Chi Alpha and Phi Chi Fraternities, and became a Fellow of the American College of Physicians in 1937.

Dr. McKibben is survived by his wife, Beryl M. McKibben of 11211 Fremont Ave., Ontario, Calif., and his mother and sister, both of whom reside in Ohio.

Dr. McKibben will be greatly missed in Ontario, especially by his many friends and professional acquaintances.

GEORGE C. GRIFFITH, M.D., F.A.C.P.,
Governor for Southern California, A.C.P.

DR. WILLIAM DAVIS TEWKSBURY

Dr. William Davis Tewksbury, F.A.C.P., died of a heart condition at his home, Chevy Chase, Md., on Wednesday, Dec. 28, 1955.

Dr. Tewksbury, born in Hutchinson, Kans., May 7, 1885, was widely known and recognized as an authority on diseases of the chest. He was graduated from George Washington University Medical School in 1908 and began the practice of medicine that year in Washington, D. C. Becoming interested in diseases of the chest, he associated himself with the Washington Tuberculosis Hospital and became resident physician from 1908–09. From 1909 to 1911 he was Physician-in-charge of Catawba Sanatorium in Va. He returned to the Tuberculosis Hospital in Washington, D. C., as Medical Superintendent and retained that assignment from 1911 to

1920. In addition to this office he held the posts of Clinical Professor of Medicine, George Washington University School of Medicine; Physician-in-Charge of Health Department, Tuberculosis Clinic, and Consultant and Associate Professor of Medicine at Georgetown University School of Medicine.

Dr. Tewksbury was included in the rolls of "Who's Who in America"; A Fellow of American Medical Association; Fellow (1923), American College of Physicians; Fellow of the American College of Chest Physicians; Diplomate, American Board of Internal Medicine; Hippocrates Galen Medical Society, Medical Society of the District of Columbia, and past Director of the Tuberculosis Association of the District of Columbia. His fraternities were Sigma Alpha Epsilon and Phi Chi and he was a member of the Chevy Chase and Cosmos Clubs.

Dr. Tewksbury was a pioneer in the use of artificial pneumothorax, employing original methods and treatments which came to be accepted as standard procedures. He contributed valuable creative papers on pulmonary diseases to various medical publications, including the *Journal of American Medical Association* and *American Review of Tuberculosis and Diseases of the Chest.*

Dr. Tewksbury is survived by his wife, the former Susan Tidball West; two daughters, Mrs. Jane West Clementson and Mrs. Harry King; also four grandchildren, all residing in the Washington area.

Dr. Tewksbury visited his office daily until within three weeks of his death. His countless friends and patients who are grieved at his passing, nevertheless rejoice in the knowledge that he lived a full and useful life to the end.

E. Raymond Fenton, M.D.

DR. LEO E. WESTCOTT

Dr. Leo Enos Westcott, F.A.C.P., was born in Hartford, Mich., on April 13, 1886. He attended Michigan State Normal College, receiving his Teachers Life Certificate in 1907. He received his medical degree from the Detroit College of Medicine and Surgery in 1914. He entered private practice in a small Michigan town from 1914 to 1916, and after that in Gobles, Mich., from 1916 to 1925. He did postgraduate work in New York, Ann Arbor, Philadelphia, and in Detroit. He was a Voluntary Assistant at the University of Michigan Medical School from 1925 to 1926. Dr. Westcott then established his private practice in Kalamazoo, Mich., on Feb. 1, 1927 and became a member of the staff of Bronson Methodist Hospital. He was, likewise, a member of the staff of Borgess Hospital and at one time was Consultant in Internal Medicine at Pinecrest Sanitarium. During World War I he served as a First Lieutenant.

Dr. Westcott was a member of the Kalamazoo Academy of Medicine, the Michigan Trudeau Society, the Michigan State Medical Society, and the American Medical Association. He was a Diplomate of the American Board of Internal Medicine and was a Fellow (1928), and a Life Member (1946), of the American College of Physicians.

He died of hypertensive arteriosclerotic heart disease and acute myocardial infarction on November 6, 1955.

H. M. Pollard, M.D., F.A.C.P.,
Governor for Michigan, A.C.P.

DR. HARRY DAVID WILLIAMS

Dr. Harry D. Williams, F.A.C.P., one of the most prominent physicians in Trenton, N. J., died on September 7, 1955, of an esophageal lesion at Temple University Hospital in Philadelphia. He was 70 years old and he had been a Trenton practitioner for 45 years.

Dr. Williams was born in Lambertville, N. J., on March 21, 1884, the son of Da La Spencer Williams and Mary E. Trauger Williams. He received his medical degree from the University of Pennsylvania School of Medicine in 1908. His internship was at St. Francis Hospital where he attained the rank of Senior Visiting Physician before his elevation to the Emeritus Staff.

He was a Diplomate of the American Board of Internal Medicine and a Fellow (1930), and Life Member 1952 of the American College of Physicians. He held membership in the Medical Society of New Jersey, Mercer County Medical Society (former Vice President), American Medical Association, Masonic Bodies and Crescent Temple), Trenton Country Club and Skytop Club, Pa.

During World War I, he served as a First Lieutenant (MC) attached to Base Hospital 136 A. E. F. and during World War II was Internist, Advisory Selective Service Board.

Dr. Williams has been sorely missed by his many friends and colleagues. He is survived by his widow, Mrs. Elsie S. Williams, and two nieces.

Edward C. Klein, Jr., M.D., F.A.C.P.,
Governor for New Jersey, A.C.P.

CAPT. PAUL W. WILSON

Capt. Paul White Wilson, (M.C.), U.S.N. (Retired), F.A.C.P., died Feb. 15, 1956, at the Veterans Administration Hospital, Los Angeles, at the age of seventy.

Born in Keokuk, Iowa, on Dec. 28, 1885, he received his education at various universities including: 1912, the University of Minnesota Medical School; 1906, the Iowa Wesleyan University.

Capt. Wilson entered the naval service as Assistant Surgeon in the Navy Medical Corps on April 4, 1917. He was appointed Captain on July 1, 1940.

During his more than 29 years of naval service, he served with the Navy Medical Department throughout the United States and abroad, and in ships of the fleet. During World War I he served on a special assignment with the High Power Radio Detachment abroad.

On Nov. 1, 1946, Capt. Wilson received a Letter of Commendation with Ribbon, for exceptional and outstanding service to the government of the United States while serving as Medical Officer in Command of the Naval Medical School, National Naval Medical Center, Bethesda, Md., from Sept. 1, 1942, until Dec. 11, 1944, and as Medical Officer in Command of the U. S. Naval Hospital, Corvallis, Ore., from Jan. 3, 1945, to the end of hostilities in World War II.

Capt. Wilson was a member of the American Medical Association, the American Society of Tropical Medicine, Nu Sigma Nu medical fraternity, and Phi Delta Theta collegiate fraternity. He became a Fellow of the American College of Physicians in 1936.

He is survived by his wife, Mrs. Margaret von den Linden Wilson of 1028 Meadowbrook Ave., Los Angeles 19.

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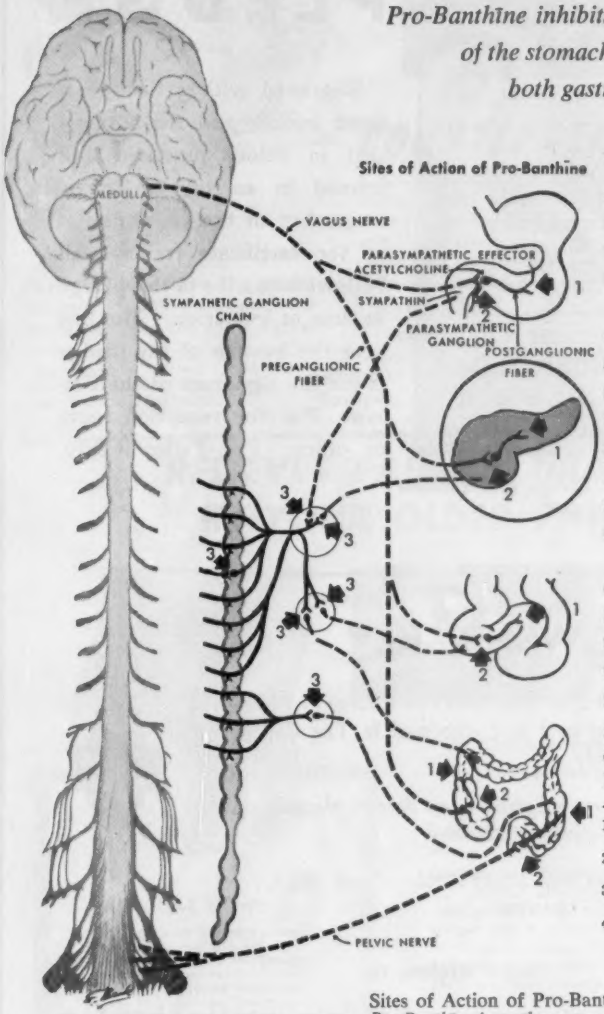

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Pro-Banthīne bromide (brand of propantheline bromide) also has proved highly effective in the therapy of peptic ulcer, hypertrophic gastritis, diverticulitis, biliary dyskinesia, ileostomies and genitourinary spasm. G. D. Searle & Co., Research in the Service of Medicine.

1. Jones, C. A.: Arch. Int. Med. *96*:332 (Sept.) 1955.
2. Zollinger, R. M.: Postgrad. Med. *15*: 323 (April) 1954.
3. Woodward, E. R.: M. Clin. North America *38*:115 (Jan.) 1954.
4. Schwartz, I. R., and Hinton, J. W.: Personal communication, February, 1955.

Sites of Action of Pro-Banthīne. *The principal site of action of Pro-Banthīne is on the parasympathetic system where it exerts a dual action while exerting a single and lesser action on the sympathetic system: (1) parasympathetic effector; (2) parasympathetic ganglion; (3) sympathetic ganglion (see arrows).*

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1. Cass, L. J. and Frederik, W. S.: Malt Soup Extract as a Bowel Content Modifier in Geriatric Constipation. Journal-Lancet, 73:414 (Oct.) 1953.

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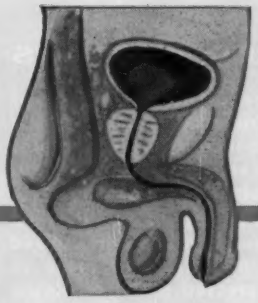

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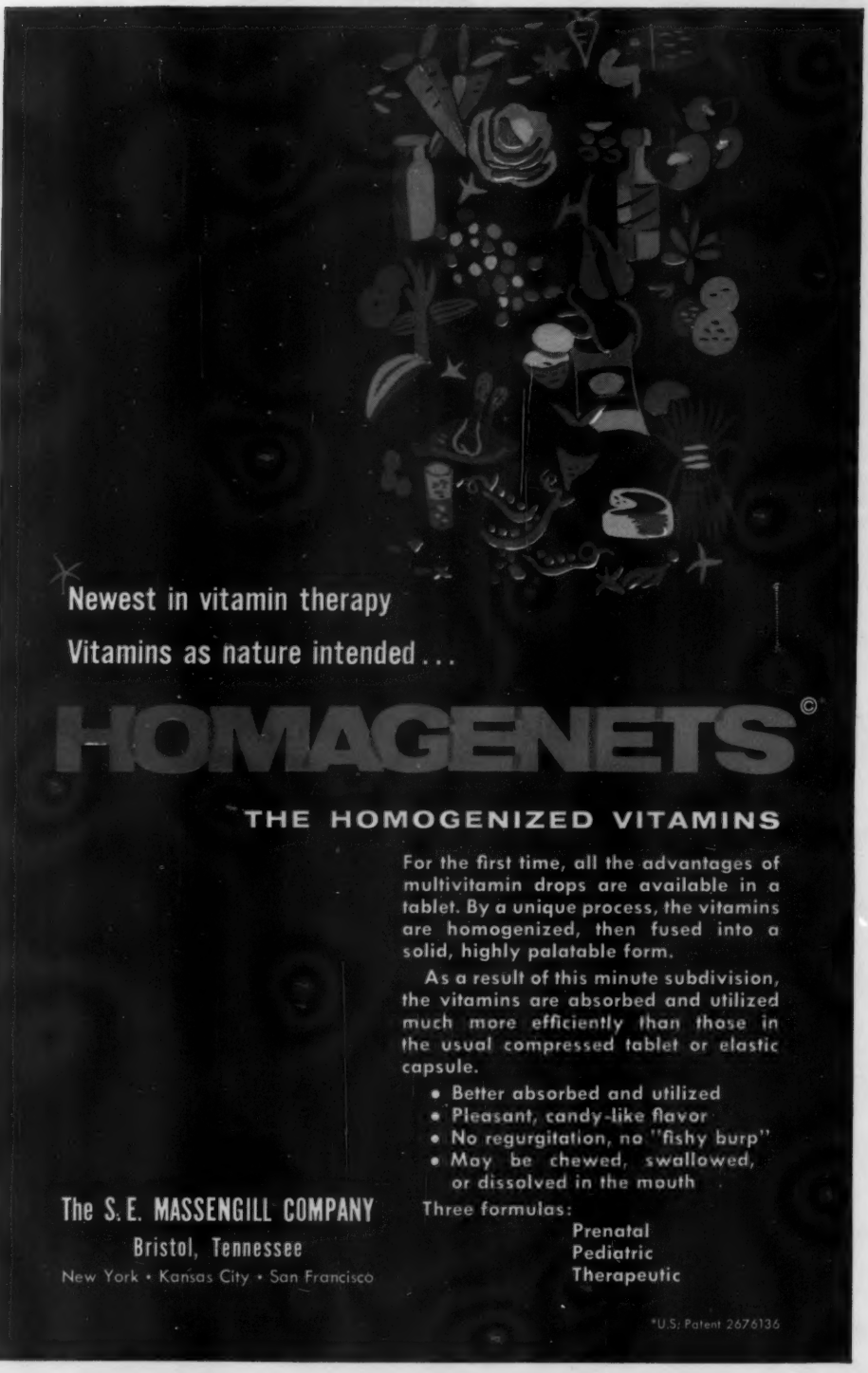
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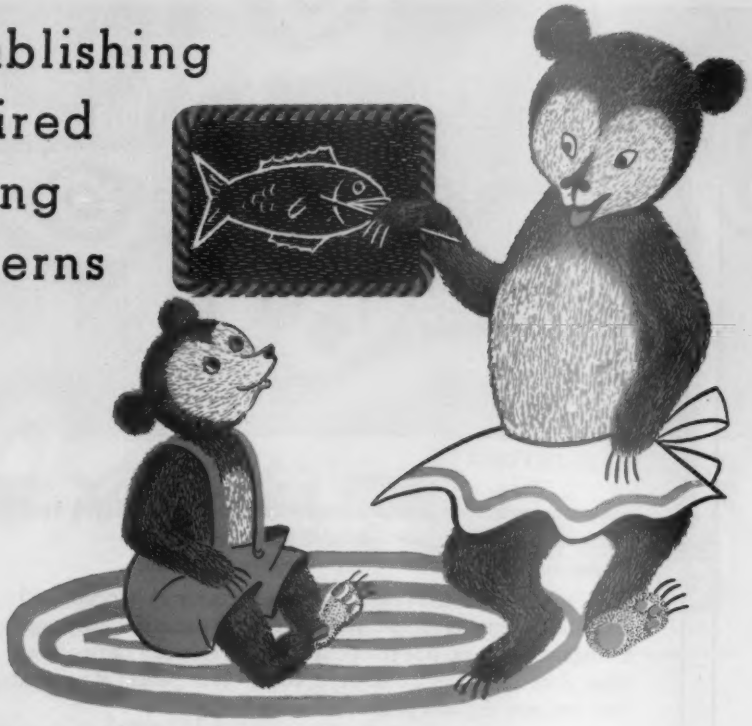
desired
eating
patterns



Obedrin®

and the 60-10-70 Basic Plan

In the development of good eating habits, medication is important, not only in initiating control, but also in maintaining normal weight.[1,2,3]

Obedrin contains:

- Methamphetamine for its anorexigenic and mood-lifting effects.
- Pentobarbital as a balancing agent, to guard against excitation.
- Vitamins B_1 and B_2 plus niacin to supplement the diet.
- Ascorbic acid to aid in the mobilization of tissue fluids.

Since Obedrin contains no artificial bulk, the hazards of impaction are avoided. The 60-10-70 Basic Plan provides for a balanced food intake, with sufficient protein and roughage.

Formula

Semoxydrine HCl (Methamphetamine HCl) 5 mg.; Pentobarbital 20 mg.; Ascorbic acid 100 mg.; Thiamine HCl 0.5 mg.; Riboflavin 1 mg.; Niacin 5 mg.

1. Eisfelder, H.W.: Am. Pract. & Dig. Treat., 5:778 (Oct.) 1954).
2. Sebrell, W.H., Jr.: J.A.M.A., 152:42 (May, 1953).
3. Sherman, R.J.: Medical Times, 82:107 (Feb., 1954).

Write for 60-10-70 Menu pads, weight charts, and samples of Obedrin.

THE S. E. MASSENGILL COMPANY
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In Congestive Heart Failure
R_x 'Wide Safety Margin'
GITALIGIN®

WHITE'S BRAND OF AMORPHOUS GITALIN

Authoritative investigators have reported that the digitalizing dose of Gitaligin is approximately one-third the toxic dose.[1-5]

This "wide margin of safety" (difference between therapeutic and toxic doses) permits rapid digitalization and successful maintenance with a minimum of toxic side reactions—even in refractory cases where other glycosides have failed.[6] And, cost to your patient is no greater than ordinary digitalis preparations.

Supplied: Scored tablets of 0.5 mg. Bottles of 30 and 100.

References: 1. Ehrlich, J. C.: Arizona Med. *12:* 239 (June) 1955. 2. Weiss, A., and Steigmann, F.: Am. J. M. Sc. *227:* 186 (Feb.) 1954. 3. Dimitroff, S. P.; Griffith, G. C.; Thorner, M. C., and Walker, J.: Ann. Int. Med. *39:* 1199 (Dec.) 1953. 4. Hejtmancik, M. R., and Herrmann, G. R.: Texas St. J. M. *51:* 238 (May) 1955. 5. Batterman, R. C.; DeGraff, A. C., and Rose, O. A.: Circulation *5:* 201 (Feb.) 1952. 6. Denham, R. M.: J. Kentucky St. M. Assoc. *53:* 209 (Mar.) 1955.

It's so easy to switch to 'wide safety margin' Gitaligin. Follow these simple dosage equivalents wherever digitalis therapy is indicated:

DIGITALIS PREPARATION	AVERAGE DAILY MAINTENANCE DOSE	GITALIGIN DOSAGE EQUIVALENT (APPROX.)
Digitalis leaf	0.1 Gm.	0.5 mg.
Digitoxin	0.1 mg.	0.5 mg.
Digoxin	0.5 mg.	0.5 mg.

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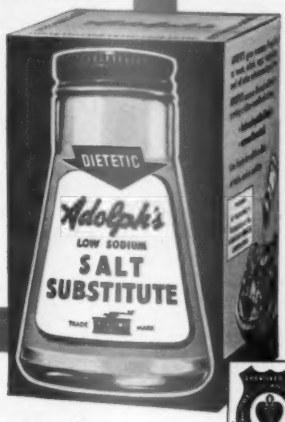

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Tetracycline *Lederle*

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The prevention and control of cellulitis, abscess formation, and generalized sepsis has become commonplace technique in surgery since ACHROMYCIN has been available. Leading investigators have documented such findings in the literature.

For example, Albertson and Trout[1] have reported successful results with tetracycline (ACHROMYCIN) in diverticulitis, gangrene of the gall bladder, tuboovarian abscess, and retropharyngeal abscess. Prigot and his associates[2] used tetracycline in successfully treating patients with subcutaneous abscesses, cellulitis, carbuncles, infected lacerations, and other conditions.

As a prophylactic and as a therapeutic, ACHROMYCIN has shown its great worth to surgeons, as well as to internists, obstetricians, and physicians in every branch of medicine. This modern antibiotic offers rapid diffusion and penetration, quick development of effective blood levels, prompt control over a wide range of organisms, minimal side effects. There are 21 dosage forms to suit every need, every patient, including

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[1]Albertson, H. A. and Trout, H. H., Jr.; *Antibiotics Annual* 1954-55, Medical Encyclopedia, Inc., New York, N. Y., 1955, pp. 599-602.

[2]Prigot, A.; Whitaker, J. C.; Shidlovsky, B. A., and Marmell, M.: *ibid*, pp. 603-607.

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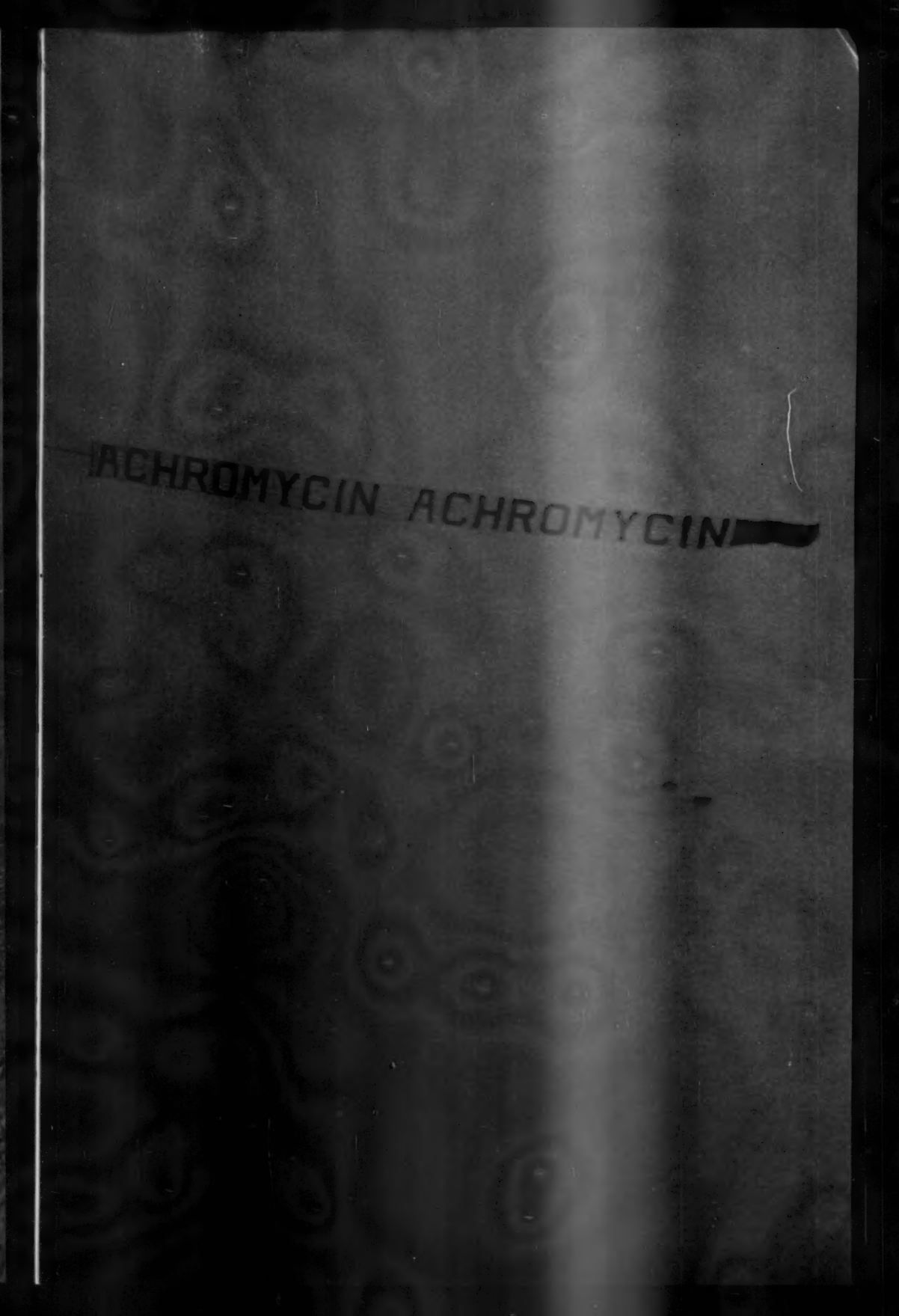
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Continued from page 58

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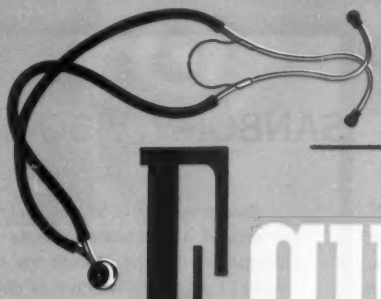
anxiety is part of EVERY ILLNESS[1]

The physically sick patient faces two stresses—the sickness and the anxiety that it brings.[1] All too often, the anxiety is a threat to the patient's progress. It may intensify symptoms, give uncertainty to therapy, and impair rapport.

To combat the anxiety component of physical illness, EQUANIL promotes equanimity, relieves muscle tension, and encourages normal sleep.[2] By these specific actions, EQUANIL gives breadth to the treatment program—expands the physician's resources.

Supplied: Tablets, 400 mg., bottles of 50.
Usual Dose: 1 tablet, t.i.d.

1. Braceland, F.J.: Texas State J. Med. 51:287 (June) 1955.
2. Lemere, F.: Northwest Med. 54:1098 (Oct.) 1955.



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anti-anxiety factor with muscle-relaxing action

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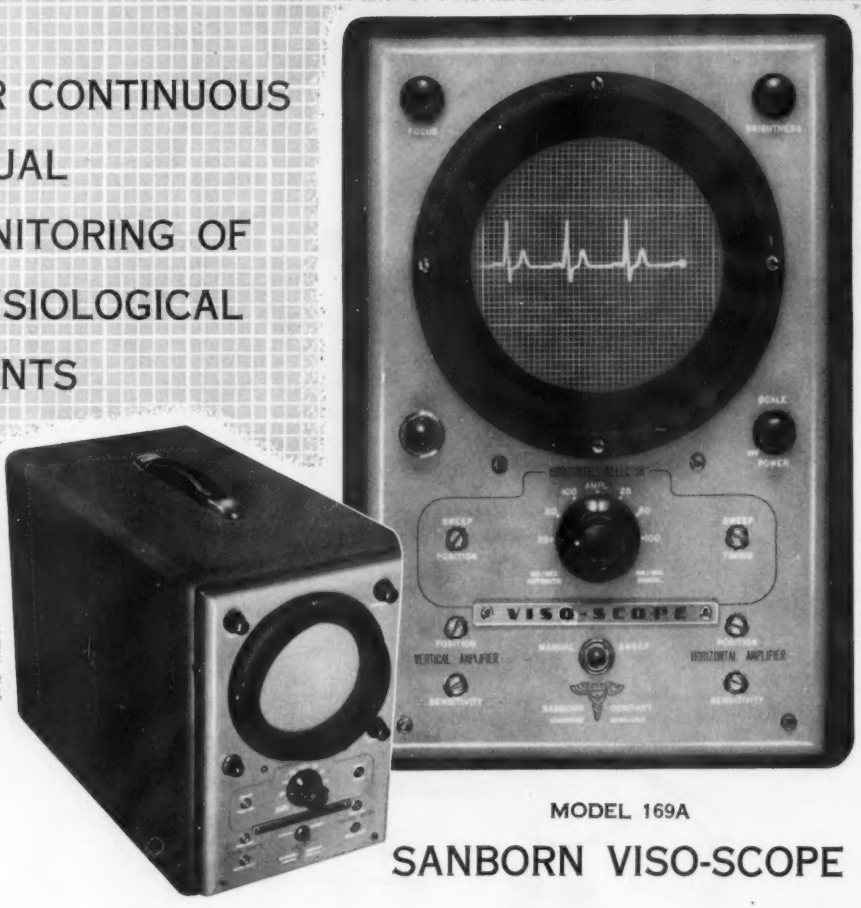


MODEL 169A
SANBORN VISO-SCOPE

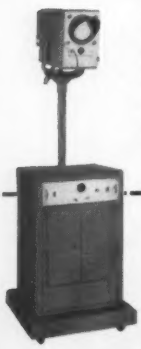
DESIGNED for compatibility with other SANBORN equipment (examples, right), simplified operation via minimum controls (illustration, above), and *precise* control of the base line sweep, the Model 169A Viso-Scope now permits the owner or purchaser of SANBORN recording instruments to greatly widen their field of usefulness.

The cathode ray tube selected for this 'scope has a ***dual coating*** which produces a beam image of exceptional sharpness and long persistence on the orange screen-filter (when monitoring) and of extreme brightness and short duration on the blue screen-filter (for photography). When photography is desired, a Fairchild or DuMont oscilloscope camera may be mounted on the screen bezel (or any common camera may be used).

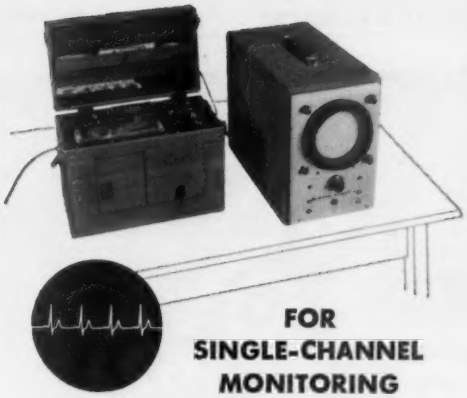
Sweep speeds of 25, 50 and 100 millimeters per second are obtainable instantaneously, and enlargement on the Viso-Scope screen of a segment of the tracing which is of particular interest may be made at any time.

Typical applications of the Viso-Scope include: observation of changes in the electrocardiogram resulting from use of drugs; pressure monitoring in catheterization during manipulation of the catheter; and a more precise study of complex wave forms by an instantaneous increasing of the sweep speed, such as in myography, phonocardiography, and small animal electrocardiography.

Descriptive literature on the Viso-Scope complete with diagrams showing hook-up requirements of various Sanborn recorders is available on request.



The Model 169A-OR (Operating Room) Viso-Scope is a completely self-contained oscilloscope-amplifier unit, specially designed for visual ECG presentation during surgery in the presence of explosive gases. Viewing unit is supported at or above five foot height on a steel column, and may be turned and tilted for best viewing angle. Provision is made for connection to a remote ECG, when written records are also desired. May also be used for display of sphygmograms, pneumograms, etc.



FOR SINGLE-CHANNEL MONITORING

Electrocardiograms may be continuously monitored with a Viso-Scope connected directly to a Sanborn Viso-Cardiette (Model 572 or 51). Or, a Model 128 or 141 Sanborn Recorder may be similarly used for viewing other phenomena such as pressure, temperature, sphygmograms, pneumograms, myograms, etc., with suitable transducers employed.

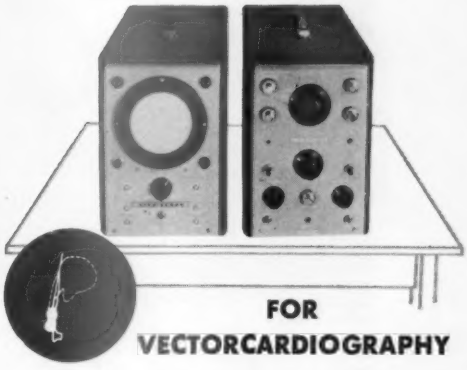
Written records may be made whenever desired during the monitoring. Selection of sweep speeds on the Viso-Scope (see left page) is particularly advantageous to owners of these instruments.

FOR MONITORING UP TO FOUR EVENTS SIMULTANEOUSLY

The Sanborn Electronic Switch, shown above connected to each channel of a Model 154M four-channel Poly-Viso, is designed for use with any Sanborn two- or four-channel *direct writing* recording system. It permits *simultaneous* observation of as many phenomena as the system is set up to record, and Viso-Scope thus connected appears to be operating with *separate beams*. Controls permit liberal relative positioning of beams on the scope screen, and *individual* sensitivity control. These adjustments have no effect on the recording instrument.

HIGHER SPEED MONITORING

With the addition of an attachable booster amplifier the Viso-Scope may be used with a Sanborn Twin-Beam Cardiette, to display phenomena of higher frequency such as are encountered in phonocardiography, small animal electrocardiography, high fidelity human electrocardiography, etc. Separate oscilloscope jacks on the Twin-Beam permit ready selection of the signal from either "phono" or ECG channel, for alternate display on the Viso-Scope screen.



FOR VECTORCARDIOGRAPHY

The Sanborn Model 185 Vector System (or vector amplifier) shown above right, has been specifically designed for use with the Viso-Scope, for displaying either vector loops or ECG complexes. This instrument's lead selector switch, together with a specially-marked 9-wire patient cable and extra electrodes, permit the instantaneous selection of either cube or tetrahedral vector leads, or ECG leads, for Viso-Scope display. Adequate sensitivity (10" per mv) provides clear showing of P and T loops, as well as QRS. Additionally (via installation of timing transformer in the Viso-Scope) the Vector system provides Z axis, or intensity modulation for indication of speed and direction of sweep trace.

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Schedule of Postgraduate Courses, Autumn, 1956

The following courses have been arranged through the generous cooperation of the directors and the institutions at which the courses will be given. Tuition fees for all courses will be: Members, $30.00; Non-members, $60.00. Full details of these courses may be obtained through the Executive Offices of the College, 4200 Pine Street, Philadelphia 4, Pa.

	October				November				December					February 1957			
	8–12	15–19	22–26	29–Nov. 4	5–9	12–16	19–23	26–30	3–8	10–14	17–21	24–29	31–Jan. 4	4–8	11–15	18–22	25–Mar. 1
Course No. 1, RECENT ADVANCES IN CARDIOVASCULAR DISEASES: Mt. Sinai Hospital, New York, N. Y.; Arthur M. Master, M.D., F.A.C.P., and Charles K. Friedberg, M.D., F.A.C.P., Co-directors.	X																
Course No. 2, SEMINARS IN INTERNAL MEDICINE: Vanderbilt University School of Medicine, Nashville, Tenn.; Rudolph H. Kampmeier, M.D., F.A.C.P., and Hugh J. Morgan, M.D., M.A.C.P., Co-directors.	X																
Course No. 3, CLINICAL NEUROLOGY: Jefferson Medical College of Philadelphia, Philadelphia, Pa.; Bernard J. Alpers, M.D., F.A.C.P., Director.		X															
Course No. 4, RECENT ADVANCES IN INTERNAL MEDICINE: University of Washington School of Medicine, Seattle, Wash.; Robert H. Williams, M.D., F.A.C.P., Director.			X														
Course No. 5, SELECTED PROBLEMS IN INTERNAL MEDICINE: University of Oklahoma School of Medicine, Oklahoma City, Okla.; Stewart G. Wolf, Jr., M.D., F.A.C.P., Director.							Thanksgiving Week	X				Christmas Week					
Course No. 6, GASTRO-ENTEROLOGY: University of Pennsylvania Graduate School of Medicine, Philadelphia, Pa.; Henry L. Bockus, M.D., F.A.C.P., Director.									3–7								
Course No. 7, ELECTROCARDIOGRAPHY: University of Utah College of Medicine and Salt Lake County General Hospital, Salt Lake City, Utah; Hans H. Hecht, M.D., Director.									X								
Course No. 8, PATHOLOGIC PHYSIOLOGY OF THE BLOOD DYSCRASIAS: Washington University School of Medicine, St. Louis, Mo.; Carl V. Moore, M.D., F.A.C.P., William J. Harrington, M.D., (Associate), and Edward H. Reinhard, M.D., (Associate), Co-directors.																X	

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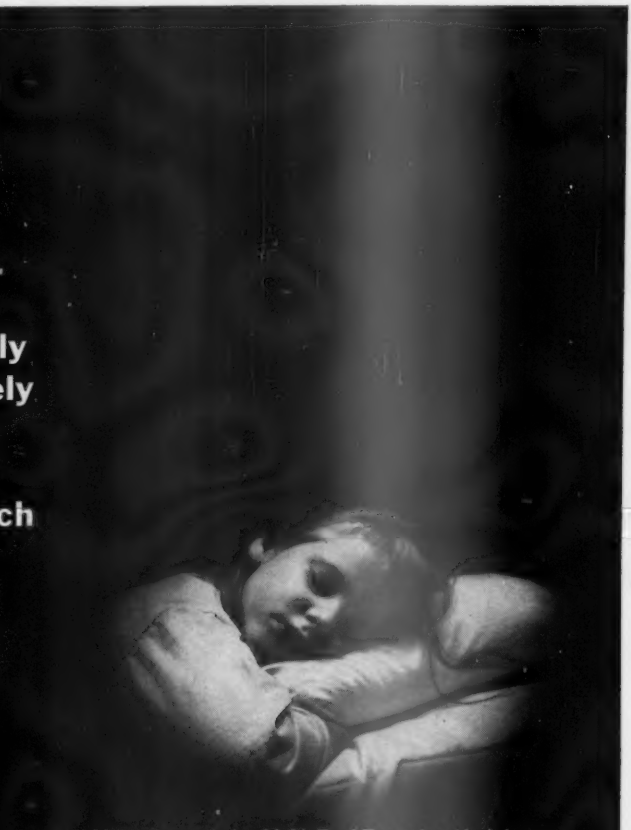

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1. Johnson, S. H., III, and Marshall, M., Jr.: A.M.A. Am. J. Dis. Child. 89:199, 1955. 2. Breakey, R. S.; Holt, S. H., and Siegel, D.: J. Michigan M. Soc. 54:805, 1955.

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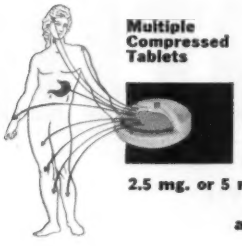

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References: 1. Boland, E. W., *J.A.M.A.* **160**:613, February 25, 1956. 2. Margolis, H. M., *et al.* *J.A.M.A.* **158**:454, June 11, 1955. 3. Bollet, A. J., *et al.* *J.A.M.A.* **158**:459, June 11, 1955.

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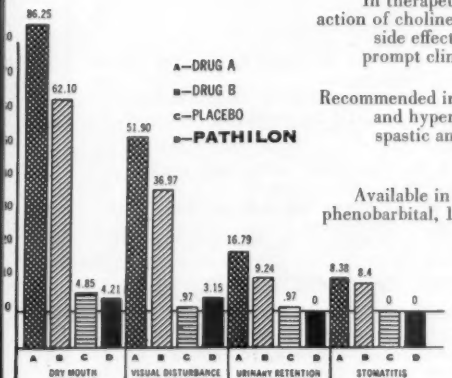

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1. Council on Pharmacy and Chemistry, J.A.M.A. 160:389 (Feb. 4) 1956. 2. "Evaluation of Drugs in the Treatment of Peptic Ulcer," by J. M. Ruffin, M.D.; D. Cayer, M.D.; J. S. Atwater, M.D., and B. G. Oren, M.D., Exhibit at A.M.A. Meeting, Atlantic City, June, 1955.

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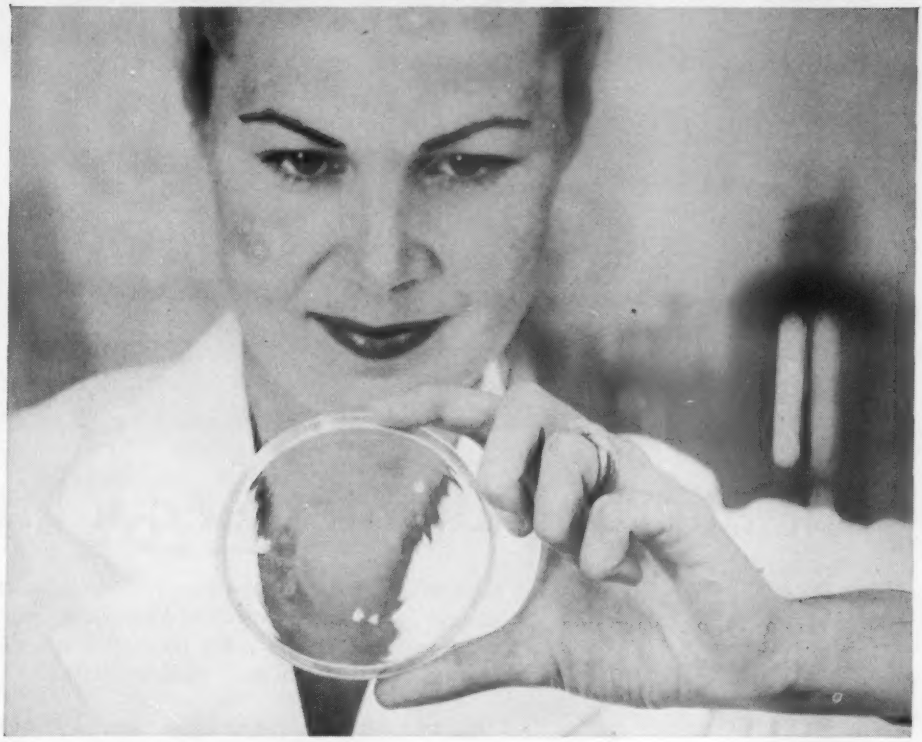

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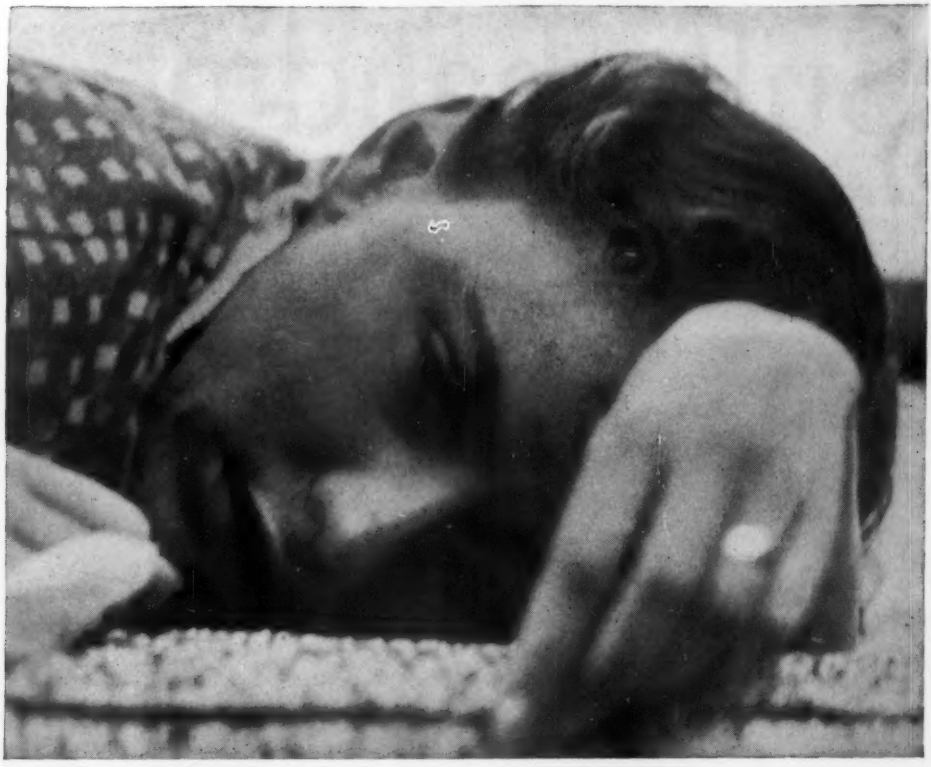

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